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Arterio-venous Fetoplacental Vascular Geometry and Hemodynamics in the Mouse Placenta

Monique Y. Rennie¹, Lindsay S. Cahill¹, S. Lee Adamson^{2,3,4}, and John G. Sled^{1,2,4,5}

¹Mouse Imaging Centre, The Hospital for Sick Children, Toronto, Ontario, Canada

²Translational Medicine, The Hospital for Sick Children, Toronto, Ontario, Canada

³Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada

⁴Department of Obstetrics and Gynecology, University of Toronto, Toronto, Ontario Canada

⁵Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada

Abstract

Introduction—The fetoplacental vasculature network is essential for the exchange of nutrients, gases and wastes with the maternal circulation and for normal fetal development. The present study quantitatively compares arterial and venous morphological and functional differences in the mouse fetoplacental vascular network.

Methods—High resolution X-ray micro-computed tomography was used to visualize the 3D geometry of the arterial and venous fetoplacental vasculature in embryonic day 15.5 CD-1 mice (n=5). Automated image analysis was used to measure the vascular geometry of the approximately 4100 arterial segments and 3200 venous segments per specimen to simulate blood flow through these networks.

Results—Both the arterial and venous trees demonstrated a hierarchical branching structure with 8 or 9 (arterial) or 8 (venous) orders. The venous tree was smaller in volume and overall dimensions than the arterial tree. Venous vessel diameters increased more rapidly than arteries with each successive order, leading to lower overall resistance, although the umbilical vein was notably smaller and of higher resistance than these scaling relationships would predict. Simulation of blood flow for these vascular networks showed that 57% of total resistance resides in the umbilical artery and arterial tree, 17% in the capillary bed, and 26% in the venous tree and umbilical vein.

Discussion—A detailed examination of the mouse fetoplacental arterial and venous tree revealed features, such as the distribution of resistance and the dimension of the venous tree, that

Corresponding author: John G. Sled, Ph.D., Hospital for Sick Children, Mouse Imaging Centre, 555 University Avenue, Toronto, Ontario M5G 1X8 Canada, Phone: 416 813-7654 x309557, Fax: 647 837-5832, john.sled@utoronto.ca.

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Declaration of interest

Conflicts of interest: none

were both morphologically distinct from other vascular beds and that appeared adapted to the specialized requirements of sustaining a fetus.

Keywords

Arteries; Fetoplacental vasculature; Hemodynamics; Micro-computed tomography; Mouse; Veins

INTRODUCTION

In the adult circulation, arteries and veins differ in both function and structure. Smooth muscle in the walls of arteries mediate autoregulation of blood flow and are organized in a manner that provides for a large pressure drop and low transit time between the major conduit vessels and the capillary bed. Veins by comparison are highly compliant with little or no contractile function, present low hemodynamic resistance and operate under low blood pressure conditions. The placenta has a number of differences from adult organs both in how it functions and how it is constructed that could provide insight into its unique architecture. In humans, the placenta is hemochorial [1] with two distinct (fetal and maternal) circulations. Exchange of oxygen and nutrients occurs between fetoplacental capillaries within the placental villi and maternal blood within the intervillous space. From a hemodynamic perspective, an important functional requirement is that the fetoplacental capillaries maintain adequate internal pressure to avoid being collapsed by the maternal blood pressure [2]. Another hemodynamic consideration is that the fetoplacental vasculature is separated from the fetal circulation by the long conduit vessels of the umbilical cord, typically 50–60cm long in humans [3], and presenting a non-negligible hemodynamic resistance [4]. Functionally, it is not clear that the fetoplacental vessels autoregulate blood flow. Another unique aspect of the placenta is that it develops and matures rapidly to keep pace with the requirements of the growing fetus. The arterio-venous oxygen gradient in the fetoplacental circulation is also reversed with respect to other organs aside from the lung. In the placenta, deoxygenated blood enters from the arteries, receives oxygen from the maternal circulation via the fetoplacental capillaries, and delivers oxygen to the fetus via the umbilical vein. These differences from other organs motivate a closer examination of how arterial and venous vessels are organized in the placenta. While the organization and hemodynamic characteristics for the fetoplacental arteries have been described, less is known about the overall network structure that includes the venous vessels.

3D imaging of the placenta using X-ray micro-computed tomography (micro-CT) has been used by a number of groups to investigate the structure of the fetoplacental arterial tree [5–7]. Venous structure, while also amenable to 3D imaging [8], has been largely unstudied. The considerations of resolution, placental size, and vessel dimensions as well as the practical aspects of obtaining samples under highly controlled experimental conditions make this technology particularly amenable to examining the mouse placenta. Moreover, computational analysis methods enable detailed measurement and hemodynamic modelling based on these 3D images [9, 10]. While the mouse and human placenta differ, most importantly in size and also the organization of the human placenta into subunits (cotyledons), there are important similarities [11, 12]. Specifically, the mouse placenta is hemochorial and shares many common structural characteristics, cell types, genetic

pathways, and functions with humans [1]. Here we present a structural and hemodynamic analysis of the fetoplacental vasculature in the mouse with the goal of understanding the structure of this vascular bed in light of its unique functional requirements.

MATERIALS AND METHODS

Mice

Experimental procedures were approved by the Animal Care Committee of the Toronto Centre for Phenogenomics and conducted in accordance with guidelines established by the Canadian Council on Animal Care. CD-1 mice were purchased from Charles River Laboratories (Montreal, QC, Canada). Males were mated in-house with virgin females aged 8–14 weeks and the morning that a vaginal copulation plug was detected was designated embryonic day (E) 0.5. All dams were euthanized at E15.5. This gestational age was chosen based on the relative ease of sample preparation; there is a higher rate of perfusion failure at E13.5 because of fragile vessels and after E17.5 the vessels are prone to vasospasm [8].

Injection of contrast agent

Detailed methods for preparing the fetoplacental vasculature for micro-CT imaging have previously been described [13, 14]. E15.5 conceptuses were surgically exposed and a double lumen cannula [13] was inserted into either the umbilical artery for arterial only perfusions or into the umbilical vein for venous only perfusions. The alternate vessel was nicked to serve as a vent. Blood was cleared from the vasculature using heparinized saline containing xylocaine [13]. Contrast agent (MV-122 Microfil, Flow Tech Inc., Carver, MA, USA) was then manually infused until it was seen entering the capillary bed. The umbilical vessels were ligated to maintain pressure during polymerization, after which placentas were immersed in formalin and later mounted in agar.

Micro-CT imaging and vascular segmentation

3D datasets were acquired for fetoplacental arterial (n=5) and venous (n=5) contrast-enhanced specimens with the surrounding tissue still intact using a Skyscan 1272 micro-CT scanner (Skyscan, Belgium). With the X-ray source at 50 kV and 201 μ A, the specimen was rotated 360° in 0.4° increments, generating 900 views in ~2 hours which were reconstructed into data blocks with a 13.4 μ m voxel size. Vascular surface renderings were generated from micro-CT data to visualize the arterial or venous vasculature [8].

The arterial or venous vasculature was automatically segmented, identifying vessel segments and bifurcations using an algorithm as previously described [15]. The algorithm returned the centre lines of a connected vessel tree and a tubular model for which the lengths, diameters, and connectivity of each vessel segment were described. Measurements of vessel segment numbers, diameter scaling coefficient, and the distribution of vessel diameters were extracted from the resultant tubular models for all vessels > 35 μ m [10, 15, 16]. Branching topology was assessed via Strahler ordering, a widely used method for designating levels of a tree that is based on how blood vessels connect [16]. In brief, terminal vessel segments were labeled as order one and then parent vessel segments were assigned either: (1) the

greater of the two orders for the daughter branches or (2) the order of the daughter plus one where the daughters were of the same order.

Hemodynamic modeling

Resistance was calculated based on vessel geometry through use of standard formulas for resistances in parallel and in series as previously described [15]. Hemodynamic calculations assumed 1) Poiseuille's law for flow of fluid through a pipe-like structure, 2) equal pressure at each terminal vessel, and 3) a correction factor modeling blood viscosity changes in small vessels derived using adult blood [17].

Statistical analysis

All statistical tests were performed using the R statistical software (www.rproject.org). Data from each group are reported as the mean $\pm$ the standard error of the mean (SEM) and analyzed using *t*-tests to compare arteries and veins. A value of $p < 0.05$ was taken to be significant. To assess group differences in the Strahler ordering data, a two-way ANOVA was performed with Strahler order and group (arteries vs. veins) as fixed factors. Where the ANOVA was significant, a Tukey post hoc test was performed for each order.

RESULTS

Examination of surface renderings and maximum intensity projection images of arterial and venous specimens (Figure 1A,D) revealed differences in branching pattern and tree dimensions. A dichotomous branching pattern was evident in arterial specimens (Figure 1A). The single umbilical artery branched extensively at the surface of the placenta (chorionic plate). These surface vessels further branched into the placenta to become intraplacental arteries that then branch into smaller arterioles and capillaries. The similarly sized single umbilical vein (Figure 1B) branched into two visually distinctive tree halves near the site of umbilical artery chorionic plate insertion (Figure 1D). Both halves sat superficial to the arterial vessels, exhibiting a magistral/mixed branching pattern along the chorionic plate [18]. Relative to the arterial vasculature, the venous vascular tree was 36% smaller in volume (Figure 1C, $p = 0.006$). Lower venous volume was due in part to a smaller tree span (Figure 1E, $p = 0.0001$) and the superficial nature of the venous tree which does not penetrate into the labyrinth, resulting in a tree depth half that of the arterial tree (Figure 1F, $p = 0.0003$).

Overall, venous trees contained 23% fewer vessels than arterial trees (Figure 2A,B). When the cumulative number of vessel segments was plotted as a function of diameter (Figure 2A), there was a significant increase in the number of vessels in the mid diameter range and a decrease in the smaller arterioles in the venous compared to arterial trees. To further understand these differences, branching was assessed via application of Strahler ordering and analysis of the diameter scaling coefficient, metrics which facilitate comparison between diverse tree structures. All venous trees had exactly 8 Strahler orders, while arterial trees had 8 or 9 (Figure 3). The Strahler ordering method revealed a trend towards a reduced number of order 1 (-24% , $p = 0.1$) and order 2 (-26% , $p = 0.1$) vessels (i.e. terminal, small diameter) in veins compared to arteries (Figure 3B). The number of larger order vessels did not

significantly differ. The diameters of Strahler orders 1 and 4 to 7 (i.e. terminal, medium and large diameter vessels, Figure 3C) were significantly larger in veins; however, there was no significant difference in arterial and venous vessel lengths (Figure 3E). As a result, length-to-diameter ratio was substantially smaller in veins than in arteries (by 15 to 47%) for Strahler orders 1 to 6 (Figure 3F). The diameter scaling coefficient in arterial trees was 2.9 ± 0.1 (Figure 2C), very close to the value of 3 predicted by Murray's Law and seen experimentally in many other beds. In contrast, the diameter scaling coefficient in veins was significantly lower (2.2 ± 0.1 , $p=0.0001$), indicating that vein diameters decrease more rapidly with each generation than for arteries. In summary, despite umbilical vein diameter being similar to the umbilical artery (Figure 1B), analysis of branching pattern revealed larger diameters for a given order throughout most of the venous tree (Figure 3C) and a trend towards more numerous, smaller diameter vessels in the arterial tree (Figure 3B).

The functional consequences of these structural differences were assessed via computational flow modeling and computation of arterial and venous vascular resistances and pressure gradients across the trees. Arterial tree resistance was 0.57 ± 0.12 mmHg·s/μl while that of the veins was 0.20 ± 0.06 mmHg·s/μl, $p=0.0004$. Resistances in the umbilical artery (Figure 4, 0.17 mmHg·s/μl) and umbilical vein (0.14 mmHg·s/μl) were estimated from umbilical vessel diameters (Figure 1B) and cord length measurements (Supplementary Table 1) using Poiseuille's Law.

Fetoplacental capillary resistance was calculated to be 0.22 mmHg·s/μl (Figure 4). The steps taken and assumptions made to estimate this value were as follows: (1) Resistance in a single capillary was calculated from Poiseuille's Law using previously reported fetoplacental capillary diameters [19] and assuming an average capillary length (L_{cap}) of $2 \times$ capillary tuft length (Supplementary Table 1). (2) Calculation of total capillary resistance assumed parallel arrangement of capillaries and standard formulas for resistances in parallel. The number of capillaries in a placenta (n) was calculated based on total length of capillaries (L_{total}) at this gestational age in the CD1 mouse strain (determined from our previously reported fetoplacental capillary volume data [10] assuming a similar ratio of fetoplacental capillary volume to total length to a report from a different strain [19]), divided by average capillary length ($n=L_{total}/L_{cap}$, Supplementary Table 1). Thus, total fetoplacental resistance was calculated to be 1.3 mmHg·s/μl. 57% of total resistance resided in the umbilical artery and arterial tree, 17% was in the capillary bed, and 26% was located in the venous tree and umbilical vein (Figure 4).

DISCUSSION

The present study is the first to use micro-CT, vascular segmentation, and computational flow modeling to quantitatively compare arterial and venous morphological and functional differences in the mouse placenta. To our knowledge, this study is also the first to use these techniques to determine both arterial and venous vascular resistances in any organ of any species. We found that the venous tree was smaller, most notably in depth, and had fewer vessels. The use of Strahler enabled a more detailed examination of these differences. It was remarkable that while individual specimens would vary in the total number of segments (c.f. Figure 2B), the number of orders was highly conserved with all venous trees having exactly

8 orders and arterial tree having 8 or 9 orders. The Strahler ordering system counts upwards from the smallest vessels. This provides a basis for comparison of the two trees as the smallest (order 1) arterioles and venules were within a few microns of each other in dimensions. Compared this way, vein diameters rise more rapidly with order than arteries, as reflected in the diameter scaling coefficient being smaller for veins than arteries (2.2 ± 0.1 vs. 2.9 ± 0.1). This trend in which diameter increases at an increasing rate with subsequent orders is characteristic of a self-similar or fractal structure [9]. A notable deviation from this trend was seen at the umbilical vein where the diameter was smaller than this trend would predict and was instead similar in diameter to the umbilical artery.

The number of terminal venules was comparable to the number of arterioles (arterial/venule ratio: 1.3). That these numbers would be similar is unexpected. Large differences have been reported for other vascular beds, for instance a ratio of 2.5–2.6 was observed for the cerebral cortex in Rhesus monkeys [20]. One factor that may affect this ratio in placenta is the fetoplacental arterioles being spread across a greater area of the placental disk. Taking this difference in span into account, the number of arterioles and venules per unit area closely matched (area explains approximately half the difference in the number of arterioles and venules) and suggests that the density of terminal vessels is one of the constraints on the geometry of the placenta. Space occupancy is also a factor in the efficiency of the branching structure of a vascular tree. Murray's Law [21] defines a branching geometry that minimizes hemodynamic resistance for a fixed blood volume. This theory predicts a diameter scaling coefficient of 3, close to the 2.9 ± 0.1 observed here for the arteriole tree. By comparison, the architecture of the venous tree has lower resistance than Murray's law would predict and this is gained at the cost of excess blood volume. It is important to note, however, that since the overall size of the venous tree is smaller, total venous blood volume is smaller than the arterial tree (Figure 1C), suggesting that despite the lower scaling coefficient fetoplacental veins do not have an important role in blood storage.

One of the unique advantages of high-resolution 3D imaging of the placental circulation is that it lends itself to direct computation of functional parameters such as hemodynamic resistance. This contrasts from traditional physiological techniques where resistance has been determined from in vivo measurements of pressure and flow [22]. To evaluate how the estimates of total fetoplacental resistance derived from the imaging data compared with other sources, we estimated umbilical artery flow (Q) from published Doppler ultrasound flow velocity data [23] and estimated pressure drop (P) across the fetoplacental vasculature by extrapolating from published pressure measurements [24, 25] (see Supplemental Methods). These data predicted a total fetoplacental resistance of $1.5 \text{ mmHg}\cdot\text{s}/\mu\text{L}$ in CD-1 mice at this gestational age, which is within 13% of our value of $1.3 \text{ mmHg}\cdot\text{s}/\mu\text{L}$, estimated solely on vascular geometry.

The umbilical artery and fetoplacental arteries were estimated to account for 57% of total resistance, and therefore 57% of total pressure drop across the fetoplacental vasculature. This is comparable to the 52% of total resistance attributed to small and large arteries in the adult mouse lung vasculature [26] but smaller than the 75% of total resistance estimated for rat mesenteric vasculature [27]. While the placenta bears some similarity to the lung in its function as an exchange organ, an important difference is the length of conduit vessels. The

umbilical vein contributes a non-negligible (11%) proportion of total fetoplacental resistance. Another factor that may affect the allocation of vascular resistance in the placenta is the need for the fetoplacental capillaries to have sufficient blood pressure to resist being collapsed by the pressure of maternal blood in the labyrinth (equivalent of the intervillous space in humans). The pressure in the fetal capillaries is also important in controlling fetal water volume [28]. This pressure matching constraint is in addition to the usual considerations of capillary transit times being sufficiently long to facilitate adequate gas and nutrient exchange with the maternal circulation.

The present study has a number of limitations. One is that a given placenta was used to visualize either the arterial or venous tree but not both. While this facilitates the automated image analysis approach used here, it did prevent us from examining correlations between arterial and venous geometry within specimens. Another limitation is that the measurements were obtained from perfused vascular specimens. While previous work from our group has shown close agreement between umbilical artery and vein measurements and those obtained in vivo by ultrasound [8], this approach does not reproduce the pressure gradient in the vessels that would be present with flowing blood. In addition, we are unable to measure the diameter of smaller vessels in the fetoplacental tree using ultrasound and therefore cannot directly confirm the accuracy of the ex vivo measurements of the fine structure. Finally, there is no data available for the viscosity of fetal mouse blood and therefore for the resistance calculations it was necessary to assume the viscosity was similar to adult blood. However, fetal red blood cells are known to be larger than in adults [29], resulting in a possible underestimation of vascular resistance. Moreover, factors such as vessel permeability and local hematocrit variation were neglected in the simulation.

In conclusion, the combination of 3D imaging and computational analysis presented here enabled examination of structure-function relationships that would not be accessible to conventional methods. A detailed examination of the mouse fetoplacental arterial and venous tree revealed features, such as the distribution of resistance, the dimensions of the venous tree, and correspondence between numbers of arterioles and venules, that were both morphologically distinct from other vascular beds and that appeared adapted to the specialized requirements of sustaining a fetus.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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ABBREVIATIONS

CT computed tomography

E embryonic day

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HIGHLIGHTS

- Micro-CT enables modelling of both arterial and venous vascular resistances
- Scaling rules for branching differ between fetoplacental arteries and veins
- Veins account for a significant proportion (26%) of fetoplacental resistance
- Number of branching generations is highly conserved across mouse placentas

Figure 2. Distribution and Number of Vessel Segments

(A) The cumulative number of vessel segments at a given diameter are shown for arteries (solid line) and veins (hatched line). The shaded grey area represents SEM. (B) The total number of vessel segments and (C) diameter scaling coefficient are shown for the arterial (black bars) and venous (open bars) vasculatures. Hatched black line in (C) denotes a scaling coefficient of 3, which is predicted by Murray's Law. Data shown as mean $\pm$ SEM where $n = 5$ placentas/group. * $p < 0.05$.

Figure 4.
Distribution of total fetoplacental vascular resistance determined by computational flow modeling.