Intravascular pressure and diameter profile of the utero-ovarian resistance artery network: estrous cycle-dependent modulation of resistance artery tone

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Sweeney TE, Bagher P, Bailey J, Cherra SJ 3rd, Grisafi FN, Pauli EM, Riley K, Soares S. Intravascular pressure and diameter profile of the utero-ovarian resistance artery network: estrous cycle-dependent modulation of resistance artery tone. Am J Physiol Heart Circ Physiol 293: H2937–H2944, 2007. First published August 17, 2007; doi:10.1152/ajpheart.01019.2006.—Blood flow to the ovary varies dramatically in both magnitude and distribution throughout the estrous cycle to meet the hormonal and metabolic demands of the ovarian parenchyma as it cyclically develops and regresses. Several vascular components appear to be critical to vascular regulation of the ovary. As a first step in resolving the role of the resistance arteries and their paired veins in regulating ovarian blood flow and transvascular exchange, we characterized the architecture and intravascular pressure profile of the utero-ovarian resistance artery network in an in vivo preparation of the ovary of the anesthetized Golden hamster. We also investigated estrous cycle-dependent changes in resistance artery tone. The right ovary and the cranial aspect of the uterus in 26 female hamsters were exposed for microradiographic observations. Estrous-cycle phase was determined in each animal before experimentation. The utero-ovarian vascular architecture was determined and resistance artery diameters were measured in each animal by video microscopy. Servo-null intravascular pressure measurements were made throughout the uteroovarian arterial network in 11 of the animals. Architectural data showed a complex anastomotic network jointly supplying the uterus and ovary. Resistance arteries showed a high degree of coiling and close apposition to veins, maximizing countercurrent-exchange capabilities. Arterial pressure dropped below 60% of systemic arterial pressure before the arteries entered the ovary. Both the ovarian artery and the uterine artery, which jointly feed the ovary, showed cycle day-dependent changes in diameter. Arterial diameters were smallest on the day following ovulation, during the brief luteal phase of the hamster. The data show that resistance arteries comprise a critical part of a complex network designed for intimate local communication and control and suggest that these arteries may play an important role in regulating ovarian blood flow in an estrous cycle-specific manner.

BLOOD FLOW REGULATION PLAYS a critical role in ovarian physiology, from meeting ovarian nutrient and oxygen demands to disseminating the hormones that regulate ovarian and reproductive function (8). This study addresses the vascular determinants of ovarian function by assessing intravascular pressure and estrous cycle-dependent changes in diameter among the arteries supplying the ovary of the female Golden hamster.

The ovary experiences up to threefold changes in blood flow amplitude throughout the estrous cycle (11, 35), with still greater increases during pregnancy and pseudopregnancy (2, 22). Total ovarian blood flow peaks during the preovulatory phase, when follicular growth is rapid and estrogen levels are high (11, 35). With ovulation and the commencement of luteal function, total ovarian flow begins to fall and initially is delivered predominantly to the corpora lutea before shifting to the next cohort of growing follicles following luteal regression (11, 35).

Several vascular components appear to be critical to vascular regulation of the ovary. The ovarian resistance arteries, which in many species anastomose with major vessels of the uterus, may help regulate ovarian flow magnitude and ovarian capillary pressure. Together with paired veins and lymphatics, they also may constitute an important countercurrent pathway for cross-regulation of the ovary and uterus (3, 14, 19). Ovarian arterioles that reside in stromal tissue may modulate flow distribution to the follicles and corpora lutea. Follicular and luteal capillaries, which undergo a dramatic change in number and distribution throughout the estrous cycle (9), clearly affect the capacity for exchange in these ovarian compartments.

Although the coarse outline of these hemodynamic changes is known, it is not clear how modulation of ovarian flow and its changing distribution are brought about, nor which segments of the vascular pathway most contribute to flow control. Our previous observations indicate that the terminal arterioles feeding follicular and luteal capillaries have little tone (30). Larger upstream arterioles reside deep in the ovary, hidden from observation. Capillary angiogenesis, so predominant in the ovary (9), may strongly affect intraovarian blood flow distribution, but capillary beds typically account for only a small percentage of total vascular resistance (13, 24). Recent evidence also has shown that uterine artery endothelium is responsive to estrogen, leading to upregulation of endothelial nitric oxide synthase (eNOS) (34) and the potential for increased nitric oxide (NO) production (37), suggesting a mechanism for resistance artery control of ovarian blood flow. Moreover, there is evidence that in some pathological conditions, such as diabetes, ovulatory dysfunction may be related to defects in vascular control such as decreased bioavailability of NO (26). In the testicular circulation, an embryologically
related vascular bed serving a parenchyma with many of the same transport demands as the ovary, a large proportion of the total vascular resistance resides in the resistance arteries (32). Thus we hypothesized that a large proportion of the total vascular resistance establishing ovarian blood flow amplitude resides in the utero-ovarian resistance arteries and that these vessels have the capacity to manipulate their tone, and thus manipulate total ovarian resistance, in relation to the stage of the estrous cycle.

The Golden hamster has been an important experimental model for the study of reproduction for nearly 70 years (6) because of a number of advantages it conveys. Its strong light-cycle dependency underlies the highly reproducible 4-day estrous cycle under laboratory conditions (9, 20). Furthermore, determination of the estrous-cycle phase is simple and unambiguous, with the day of estrous marked by a vaginal discharge that is so prominent and distinct (6) that it is the routine method for determining cycle phase (9, 35). Coupling these advantages with the deep body of knowledge in hamster reproductive physiology as well as the extensive use of the hamster for in vivo microcirculatory studies (7, 16, 25, 30, 32) establishes the hamster as an excellent model for the study of vascular control of reproductive function.

We have employed our in vivo preparation of the hamster utero-ovarian vascular network (30) to pursue the three following experimental objectives: 1) to characterize the architectural arrangement of the network of arteries that supply and interconnect the ovary and the uterus, 2) to quantify the intravascular pressure profile across this arterial network to estimate the resistance artery contribution to total ovarian vascular resistance, and 3) to determine whether the utero-ovarian resistance arteries modulate their diameters in an estrous cycle-specific manner.

METHODS

Animal care/reproductive status. All procedures were approved by the Institutional Animal Care and Use Committee of The University of Scranton. Twenty-six sexually mature female Golden hamsters (Mesocricetus auratus; Harlan Sprague Dawley, 67–96 days old) were used. Animals were housed in an air-conditioned (22°C) and light-cycle controlled (14:10-h light:dark cycle; lights on at 7 AM) room and used. Animals were housed in an air-conditioned (22°C) and light-cycle dependency underlies the highly reproducible 4-day light-cycle dependency underlies the highly reproducible 4-day estrous cycle. Our determination of the utero-ovarian resistance artery network architecture enabled routinely identifiable segments of the ovarian and uterine arteries to be chosen for diameter measurement.

Separate pilot experiments were performed to assess resistance artery tone in our preparation because vasodilators dramatically elevate ovarian microvascular permeability beyond its already extreme control values, causing rapid dye leakage. After control diameter measurements were obtained in these experiments, the vascular bed was maximally vasodilated via the addition of $10^{-4}$ M adenosine to the superfusate, and diameter measurements were repeated. Resistance arteries from all the locations observed in our study were found to have tone, which, expressed as percent constriction from maximum diameter, averaged $20.3 \pm 1.9$ (±SE) percent. No vessels were observed to be maximally dilated in the control state.

Microscopy. Ovarian vessels were observed with a fixed-stage microscope by using water-immersion objectives (Olympus). The vasculature was visualized by epi-illumination after intravenous injection of $2 \times 10^6$ mol wt TRITC dextran (18 mg; Research Organics). The image was captured with a low-light video system (Dage-MTI), displayed on a high-resolution monitor (Panasonic), and recorded with a Super VHS video recorder (Panasonic).

Vascular network analysis and diameter measurement. Video images were digitized from the analog recordings by using iMovie software (Apple) on Macintosh computers (Apple). Resistance artery networks were reconstructed for each animal by using Adobe Photoshop. Network and vessel dimensional measurements were made from the digitized networks by using NIH Image software. All dimensional measurements were calibrated against digitized recordings of a stage micrometer.

Microvascular network pressure profile. To establish whether utero-ovarian resistance arteries comprised a significant proportion of the total utero-ovarian vascular resistance, we determined the pressure profile by measuring resistance artery intravascular pressure in 11 animals at discrete locations along the utero-ovarian circuit, corresponding to distinct elements of the vascular architecture. To ensure that all measurements were made within a reasonable time after the induction of anesthesia, pressure was not measured at every measurement site in each animal; rather, the pressure profile was compiled from all measurements made. All measurements were made with the animals at the same depth of anesthesia and within 4–5 h of the induction of anesthesia (typically during the final 2 h of anesthesia). Twenty-five resistance artery and two uterine vein pressure measurements were made. Estrous cycle was tracked for each animal observed, and animals from each cycle day were used, but data were pooled across all cycle days because preliminary data indicated that cycle day-specific differences in pressure within the resistance artery network would not be resolvable. An IPM model 4A servo-micro-pressure system was used with triple-beveled glass micropipettes. Pipettes were polished to 1–2 μm outer diameter on a WPI beveler coated with 0.3 μm alumina abrasive film. To visualize the pipettes under epifluorescence illumination, Acridine red (125 μg/ml; Polysciences) was added to the 2 M NaCl solution used to fill the pipettes. Pipettes were calibrated before and after each measurement. Pressure data were acquired and analyzed by using a MacLab data-collection system (ADInstruments) and a Macintosh computer (Apple). Systemic pressure measurements were collected simultaneously with each servo-null pressure measurement and in each case showed the same periodicity generated by the cardiac cycle. Servo-null pressure measurements are presented normalized against their simultaneously determined systemic arterial pressure measurement. To the extent that diameter measurements are reported from vessel segments on which servo-null pressure measurements were performed, the diameters reported reflect the diameters observed during the pressure recording.

Resistance artery diameter measurements sites. Resistance artery diameter was measured and compiled for each day of the hamster estrous cycle. Our determination of the utero-ovarian resistance artery network architecture enabled routinely identifiable segments of the ovarian and uterine arteries to be chosen for diameter measurement.
Three segments were chosen along the ovarian artery and were designated the upper coils, middle, coils and lower coils (Fig. 1C). Two uterine artery segments were chosen, one located just distal to the separation of the uterine artery and vein (Fig. 1C) and one located just distal to the “symmetrical bifurcation” (Fig. 1C). (Additionally, diameter was recorded to accompany pressure measurements made at the ovarian insertion point, where the ovarian and uterine arteries join; these data were not separated by cycle day.) To allow cataloguing and spatial comparison of measurements made in each animal, the vascular pathway was traced in each digitally reconstructed network and numbered hash marks were made each 1,000 μm, as shown in Fig. 1A.

Statistical analysis. Data are presented as means ± SE. Vessel diameters from each day of the 4-day estrous cycle were compared by single-factor ANOVA, with post hoc comparisons among pairs of means by Tukey’s test (33). Statistical outliers were determined by using Tukey’s test (33). Application of the outlier test resulted in the exclusion of 1 out of a total of 109 diameter data points. Significance was assessed by using 95% confidence limits.

RESULTS

Vascular architecture. We reconstructed the intricate utero-ovarian resistance artery network from digitized video and spatially characterized the resulting montages (Fig. 1). Figure 2 provides a color-coded, schematized version of the network shown in Fig. 1C that clarifies the identity of arteries and veins and typical features of the utero-ovarian network. The vascular network possessed an architectural complexity that is typically confined to arteriolar networks. It was characterized by a high degree of arterial coiling that maximized contact with the closely juxtaposed veins (see OA and OV in Fig. 2 as well as Fig. 1B), unusually small arterial diameters at particular locations within the network, and multiple anastomoses between the ovarian and uterine arteries (see “symmetrical bifurcation” in Fig. 2 and sites labeled “A” in Fig. 1, A and C).

There existed two distinct arterial feeds to the ovary, the uterine and ovarian arteries (UA and OA, respectively, Fig. 2). The uterine artery arose from the iliac artery and was paired with the uterine vein until ~9,000 μm from the ovary (separation point, Fig. 1C). It then followed a smaller venous branch, coiled or curved to varying degrees, eventually bifurcated symmetrically (Fig. 2; Fig. 1C) after giving rise to a number of smaller side branches, and experienced an abrupt decrease in diameter before joining the ovarian artery and

[Image 53x310 to 413x721]
entering the ovary (IP, Fig. 2). The ovarian artery arose from the abdominal aorta and followed a straight-line path with the ovarian vein until \( \approx 10,000 \mu m \) from the ovary. At this point, it underwent dramatic coiling (OA, Fig. 2) as well as abrupt diameter changes at (typically) symmetrical bifurcations that occurred more distally along the uterine artery. Pressure changed little with distance across the proximal uterine artery segments, where diameter was quite constant along the length of the segment (Fig. 1C; artery/vein separation). On average, pressure changed here by \(< 1 \text{ mmHg} \) across a distance of \( 2,500 \mu m \) (data not shown). It was in the most distal \( \approx 1,000 \mu m \) of the uterine artery, from the point of the symmetrical bifurcation identified in Fig. 2 to the insertion point into the ovary (IP, Fig. 2), that diameter and intravascular pressure both dropped sharply.

**Resistance artery diameter throughout the estrous cycle.** Because servo-null pressure measurements indicated that a significant proportion of the total ovarian vascular resistance resided in the resistance arteries, we examined the possibility that the resistance arteries altered their diameter in an estrous cycle-dependent manner. We focused our cycle-dependent measurements on vessel diameter rather than intravascular pressure because of the much clearer and stronger relationship of diameter to modulation of vascular resistance.

Changes in resistance artery diameter correlated with the 4-day hamster estrous cycle in segments of both the uterine and ovarian arteries, with the smallest diameters occurring on cycle day 1, following ovulation, which occurs during the early-morning hours of cycle day 1 (35). Cycle day-specific arterial
diameters at prominent network locations are shown in Fig. 3. Along the uterine artery, vessel diameter at the point of separation of the artery and vein (Fig. 1C) changed significantly with estrous cycle day. Day 1 and day 2 diameters, 209 ± 9 μm and 217 ± 8 μm, respectively, were significantly less than the day 3 diameter, 260 ± 9 μm. At the point just distal to the symmetrical bifurcation of the uterine artery identified in Fig. 1C, there were no day-specific differences in arterial diameter (Fig. 3); diameter here averaged 143 ± 5 μm across the four cycle days. Arterial diameter dropped further from this point to the point of insertion into the ovary, where it averaged 62 ± 2 μm.

Ovarian artery diameter at the lower coils (Fig. 1C) also changed significantly with estrous cycle day. As with the uterine artery, vessel diameter was smallest on cycle day 1. Lower-coil mean diameter on day 1 (48 ± 4 μm) was significantly less than the mean diameters on day 2 (99 ± 9 μm) and day 3 (87 ± 5 μm). The day 4 lower-coil mean diameter (71 ± 11 μm) was not significantly different from the diameter on any other cycle day. In the upper and middle coils of the ovarian artery, there were no significant changes in diameter with cycle day. Across the 4 days of the cycle, upper coil diameter averaged 231 ± 6 μm and middle coil diameter averaged 125 ± 6 μm. It is interesting to note that for the two vessel segments that showed significant cycle-dependent diameter changes, the temporal pattern of diameter change was not identical (Fig. 3). Although both the uterine artery and ovarian artery segments were smallest in diameter on day 1, in the uterine artery, the day 2 diameter was the most similar to the day 1 diameter, yet in the ovarian artery, the day 2 diameter was the most different from the day 1 diameter.

**DISCUSSION**

We have established the potential of the utero-ovarian resistance artery network to participate in the control of ovarian blood flow and the humoral coordination of the estrous cycle. We characterized the network architecture and determined the intravascular pressure profile and estrous cycle day-specific changes in tone of the network resistance arteries. The data suggest that the utero-ovarian vascular circuit provides a specialized pathway for communication between the ovary and the uterus. Key features included a high degree of coiling of the resistance arteries that maximized surface area contact between the arteries and veins, small arterial diameters in particular network locations that increase vascular resistance and reduce intravascular pressure, and multiple interconnections between the ovarian and uterine resistance arteries and veins that permit alterations in the source and drainage of ovarian and uterine blood flow. Intravascular pressure measurements showed a sharp drop in arterial pressure before the entry of the arteries into the ovary, highlighting the large contribution of the resistance arteries to total network resistance and establishing the potential of these vessels to control ovarian blood flow amplitude. Diameter measurements at defined locations across the resistance artery network showed that segments of the uterine and ovarian arteries each exert control over ovarian vascular resistance in an estrous cycle-specific manner.

**Vascular architecture.** The hamster utero-ovarian arterial and venous network is characterized by a high degree of arterial coiling, especially along the ovarian artery, and close apposition between the arteries and veins. It also is a multiply anastomotic network that establishes shared supply and drainage between the ovary and uterus. The resistance arteries assume extremely small diameters (<100 μm) along portions of both the ovarian and uterine supply routes to the ovary, and venous diameters are large.

Comparative studies have shown that the utero-ovarian vascular architecture observed in the hamster is shared with other species, including rats, guinea pigs, cattle, sheep, and swine (for review, see Ref. 12). With variation, it is also present in rabbits and horses (12) and also has been described in women (1).

The most commonly described functional consequence of this architecture is its capacity to operate as a countercurrent exchanger for both ovarian and uterine products. The countercurrent exchanger, which also involves the lymphatics (3, 14, 19), has been cited for its role in delivering uterine-derived prostaglandin F2α (PGF2α), the luteolytic agent in many species (12, 18, 23), and for its potential to provide a concentrating mechanism for ovarian steroids (1, 21, 29).

The similarities of the utero-ovarian network to the countercurrent exchanger present between the testicular arterial and venous circulation are striking. The testicular network, which has the same embryological origins as the utero-ovarian network, serves to preserve high testicular testosterone concentrations (10). The coiled nature and small resistance artery diameter in the testicular vasculature also were associated with a large pressure drop across the resistance arteries (32), as is reported in this study for the ovarian artery.

**Resistance artery pressure profile.** Resistance artery pressure dropped steeply proximal to the arterial entry point into the ovary. The pressure drop occurred along both ovarian and uterine artery supply routes, but the profile of the pressure drop differed in the two arteries. Pressure dropped in multiple steps along the ovarian artery, whereas along the uterine artery it dropped mostly in a single large step near the artery’s termination at the ovary. Abrupt reductions in pressure along both arteries coincided with sharp reductions in arterial diameter at bifurcations that typically yielded equal-diameter daughter vessels.

The reduction of resistance artery pressure to 58% of the systemic value before the ovarian entry point establishes that a large proportion of the total resistance of this vascular bed resides in the resistance arteries. Our pressure measurements using the servo-null technique represent the most direct and least invasive in vivo pressure measurements made in this network.

An estimate of the resistance arteries’ contribution to total ovarian vascular resistance was made on the basis of the simple series resistance model first proposed by Pappenheimer and Soto-Rivera (24) and subsequently used by Gore (13) and others (5, 32). Beginning with a formula analogous to that of Gore’s (13) for determining the pre- to postcapillary resistance ratio, one can estimate the ratio of resistance before and beyond the insertion point of the resistance arteries into the ovary as

$$R_{RA} = \frac{P_{IP} - P_A}{P_V - P_{IP}}$$

where $R_{RA}$ is the resistance of the resistance arteries and $R_{Re}$ is
the remainder of the total ovarian resistance \( R_T \) that lies downstream of the resistance arteries, such that \( R_T = R_{RA} + R_{Re} \). \( P_{IP} \) is the pressure at the insertion point, \( P_A \) is the systemic arterial pressure, and \( P_V \) is the ovarian venous pressure. Then, by using the relationship

\[
\frac{R_{RA}}{R_T} = \frac{R_{RA}}{R_{Re}} \left( \frac{1}{1 + \frac{R_{RA}}{R_{Re}}} \right),
\]

one can estimate the resistance arteries’ contribution to total ovarian vascular resistance as

\[
\frac{R_{RA}}{R_T} = \frac{P_{IP} - P_A}{P_V - P_{IP}} \left( \frac{1}{1 + \frac{P_{IP} - P_A}{P_V - P_{IP}}} \right).
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The accuracy of this estimate is subject to the assumptions delineated by Pappenheimer and Soto-Rivera (24), the most relevant of which is that the utero-ovarian vascular network is not accurately described as consecutive resistive elements arranged in series, but rather as groups of parallel resistive elements arranged in series. Nevertheless, the model provides an informative first estimate of the contribution of the resistance arteries to total ovarian vascular resistance. We applied this model by using the pressure data reported here, including the uterine vein pressure of 7% of systemic pressure, which agrees well with similar venous pressure measurements we made previously in the most distal testicular veins (31, 32).

On the basis of this model, we calculate the proportion of the total utero-ovarian vascular resistance that the resistance arteries contribute to be 45%. This falls between two previous estimates: that of Reynolds (27) (50–70% of total resistance, based on hemodynamic and anatomical arguments) and that of Massa and Bruce (17) (19% of total vascular resistance, based on measurements with a 70-μm-diameter glass cannula in a ligated, venous outflow rat preparation).

The degree of pressure drop in the utero-ovarian resistance arteries was similar to that which we previously measured along the embryologically related testicular artery network (32). Both networks are characterized by coiled, small-diameter resistance arteries (36) and large-diameter veins. In the ovary, as in the testis (32), the characteristic of large venous diameters begins at the immediate postcapillary level (21). The network architecture and our pressure measurements thus suggest a high pre- to postcapillary resistance ratio in the utero-ovarian vascular network, typically leading to low capillary pressure, as we found previously in the testis (32). As in the testis, low ovarian capillary pressure would serve to hold fluid filtration in check in an exchange bed known for its incredibly high protein permeability, which becomes still higher as ovulation is approached (3, 19, 30). Although a resistance distribution such as this buffers capillary pressure changes brought about by changes in arterial pressure, it makes capillary pressure highly sensitive to increases in venous pressure (31). Even modest increases in venous pressure have been shown to cause dramatic increases in filtration and lymph formation in the ovary (3, 19).

We did not systematically assess cycle day-specific changes in resistance artery pressure. As flow amplitude changes, pressure at a given site is as likely to rise as it is to fall, dependent as pressure values are on the flow rate and the distribution of the changing resistance. In fact, one might expect that changes in pressure at a given site may be quite minimal as flow changes, as a consequence of potential autoregulatory mechanisms such as the myogenic and flow-dependent responses. Preliminary data of ours on isolated, cannulated utero-ovarian resistance arteries that show that both these mechanisms operate in this network (unpublished observations). The pressure data of the current study, preliminary as they might be in determining cycle-related changes in pressure, support the insensitivity of pressure at a given site to cycle phase. Given the fourth-power relationship between vessel diameter and vascular resistance, vessel diameter measurements are much more sensitive indicators of site-specific modulation of vascular resistance than is intravascular pressure.

**Implications for mechanisms of control of ovarian blood flow.** Ovarian blood flow has been reported to vary up to nearly threefold throughout the estrous cycle, with peak flow occurring during the preovulatory phase and flow decreasing during the luteal phase (11, 35). Larger increases in ovarian flow occur with pregnancy or pseudopregnancy (2, 22). Intraovarian vascular changes, including cyclical angiogenesis, certainly contribute to the change in ovarian blood flow (9). Nevertheless, because such a large proportion of the total vascular resistance resides in the utero-ovarian resistance arteries, we investigated the role of resistance artery diameter changes in the cyclical change in ovarian vascular resistance.

Our data showed that the resistance arteries feeding the ovary changed diameter in sync with the estrous cycle, with minimum diameters occurring in the postovulatory period. The diameter of the most proximal uterine artery segment we measured was reduced by 17–20% on cycle days 1 and 2, compared with the peak diameter on day 3. All segments of the uterine artery that we measured were distal to the portion of the uterine artery that feeds that uterus and as such represent the ovarian feed vessel emanating from this supply. Along the other supply route, the lower coils of the ovarian artery showed a more striking change, where the day 1 diameter was 45–52% smaller than the peak diameters on days 2 and 3. The cyclical progression of changes in uterine and ovarian artery diameter were not completely in sync; uterine artery diameter peaked on day 3, whereas ovarian artery diameter peaked on day 2.

It is difficult to quantitatively estimate how the observed changes in resistance artery tone alter ovarian blood flow because blood flow was not measured in this study. Nevertheless, hemodynamics dictate that the lower coils of the ovarian artery should contribute the greatest proportion of vascular resistance along this supply route, because their length is similar to larger-diameter upstream segments, yet their diameter is smallest. They also were the ovarian artery segments that showed the greatest cyclical changes in diameter. The increase in tone of the lower ovarian coils late in cycle day 1, which most likely alters flow amplitude, may have the additional effect of altering the ovarian hormonal milieu by shifting the source of ovarian blood flow to the uterine feed. The overall effect on the source of ovarian flow is uncertain, however, because the proximal segment of the uterine artery that we observed also had its smallest diameter on day 1. At this time in the cycle, the uterus is releasing the putative luteolytic agent PGF2α, which is delivered to the ovary via a countercurrent-exchange mechanism involving uterine venous

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and lymphatic vessels and the uterine artery (12, 18, 23). Chaichareon and colleagues (4) documented variability in the relative contributions of the uterine and ovarian arteries to ovarian blood flow in the guinea pig and suggested that it reflected competing effects of the local mediators of blood flow. Along the uterine artery supply route, it is likely that the long segment proximal to the symmetrical bifurcation is most influential in cyclically altering the ovarian blood supply from this source. Although this segment is larger in diameter than the segment beyond the symmetrical bifurcation, it is many times longer, increasing its influence on flow amplitude as it cyclically changes its tone. The segment distal to the symmetrical bifurcation, which did not show cyclical changes in tone, may be more critical to dropping pressure than controlling flow, because it was across this segment of the uterine artery pathway that pressure dropped most precipitously.

Reconciling the cyclical changes in tone that we observed with ovarian blood flow measurements made previously by other investigators (11, 35) is made difficult by a number of factors. Among these are the complexity of the vascular network, the duality of blood flow sources, and the exclusion of inflow or outflow pathways in prior assessments of ovarian blood flow (11, 35). The most consistent temporal relationships are the large diameters and peak flows in the immediate preovulatory period and, in the case of Varga and Greenwald’s data (35), the sharp falloff in flow on day 1 that parallels the vasoconstriction that we observe. In other phases of the cycle, vessel tone and blood flow data are difficult to correlate, especially because changes in tone in the uterine and ovarian arteries are not always in sync with one another. Although it is appealing to link the rise and fall in flow and diameter to estradiol levels (11, 35), the temporal relationship between estradiol, resistance artery diameter, and measured ovarian blood flow also are not wholly consistent.

Neural influences on cyclical changes in utero-ovarian blood flow have been considered. Estrous cycle-linked changes in uterine innervation have been documented in the rat (38). However, the axonal degeneration and regeneration observed was isolated to the uterine myometrium and was observed not to affect uterine vascular innervation. In the hamster, the majority of uterine sympathetic innervation is indeed directed to affect uterine vascular innervation. In the hamster, the major arteries supplying the ovary of the pregnant rat. Nature New Biology 238: 129 –134, 1972.


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