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Research Article

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The Effect of Changes in Perfusion Pressure on Uteroplacental Blood Flow in the Pregnant Rabbit

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ABSTRACT The effect of perfusion pressure on uteroplacental blood flow was determined in pregnant rabbits utilizing the radioactive microsphere method. Control mean arterial pressure, 93 mm Hg±2.6 SEM, was raised by carotid ligation to 109±4.1 mm Hg and then reduced with antihypertensive drugs to 74±1.3 mm Hg. Over this range of pressure there was no significant change in cardiac output, 605±36, 523±37, and 540±39 ml/min; or uteroplacental blood flow, 30±3.2, 27±5.2, and 29±4.5 ml/min, respectively. When prostaglandin synthesis was inhibited with either indomethacin or meclofenamate (2 mg/kg), uterine vascular resistance was higher but maintenance of uteroplacental flow occurred over a perfusion pressure of 89±6.7–115 ±9.3 mm Hg. With more severe hypotension induced with trimethaphan, control arterial pressure fell from 92±2.4 to 39±0.9 mm Hg, cardiac output fell from 514 ±17 to 407±22 ml/min ($P < 0.025$) and uteroplacental blood flow fell from 6.1±0.9 to 2.5±0.9% of cardiac output ($P < 0.05$), which represented an absolute fall from 32.4±5 to 10.6±3 ml/min ($P < 0.025$). There was no significant change in renal blood flow expressed as percentage of cardiac output, 14.9±2 and 13±1.5%, or in absolute flow, 75±7.7 and 54±7 ml/min with trimethaphan-induced hypotension.

These studies indicate that uteroplacental blood flow is maintained relatively constant over a range of perfusion pressure of 60–140 mm Hg in both normal and prostaglandin-inhibited pregnant rabbits. However, with reduction in pressure to 36–42 mm Hg, uteroplacental blood flow falls, expressed as a percentage of cardiac output and in absolute flow.

INTRODUCTION

The effect of arterial pressure on uterine blood flow is unclear. Previous studies in pregnant ewes have suggested failure of the uterine circulation to regulate flow; as if the uterine vascular bed acted like a series of rigid tubes, flow being proportional to perfusion pressure (1, 2). If the uterine circulation of the human behaves similarly, there would be important clinical implications in the development of hypertension and its treatment during pregnancy. However, the ewe, which has been utilized for studies of the uterine circulation, has species differences which makes application of the results to the human uterine circulation difficult. The placental implantation of the ewe is different from the human and, unlike the human, the uterus and placenta of the ewe does not contain renin (3). Since it has been postulated that uterine renin may be involved in regulating uterine blood flow during pregnancy, possibly by increasing prostaglandin E synthesis, this difference may be significant (4). Previous studies of uterine blood flow have also been hampered by the existence of multiple arteries to the organ and the tendency of the uterine artery to vasoconstrict when flow probes are attached to them. We have recently reported a method for measuring uteroplacental blood flow in the pregnant rabbit which avoids problems inherent with manipulation of the uterus (5). The results are reproducible and the blood flows obtained compare favorably with direct measurements of the uterine blood flow in this animal (6). Because the placental implantation of the rabbit is similar to human, and the rabbit uterus can synthesize renin (7), studies of the effect of perfusion pressure on uteroplacental blood flow were conducted in this animal.

METHODS

Experiments were performed on 3.5- to 5-kg New Zealand white rabbits studied between the 23rd and 29th day of gestation. The animals were anesthetized with pentobarbital. A tracheostomy and catheterization of the left jugular vein and right carotid artery were performed, with the catheter advanced into the left ventricle. Confirmation of the placement of the catheter was made by obtaining a left ventricular pressure tracing. An additional catheter was placed in the right femoral artery to monitor blood pressure and col-

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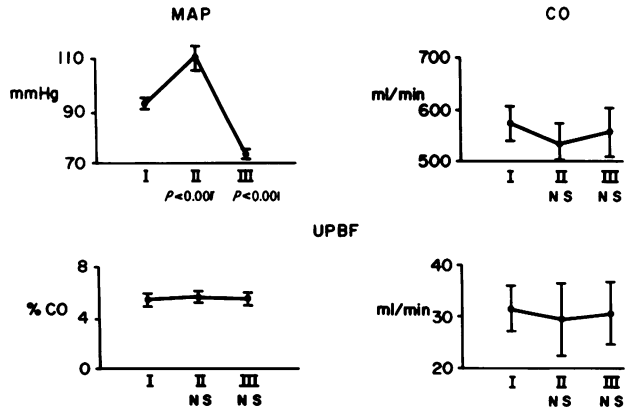

FIGURE 1 The effect of variation in MAP on CO and UPBF expressed as a percentage of (%) CO and in milliliters per minute. Period I, control; period II, carotid ligation; and period III, administration of antihypertensive drug.

lect blood samples. A femoral vein was catheterized in most animals, and the catheter was advanced to the inferior vena cava below the renal veins but cephalad to the entrance of the common iliac veins. Its placement was checked by dissection at the end of the procedure. Blood samples collected from this site were used to measure inferior vena cava prostaglandin E concentration.

Cardiac output and uteroplacental blood flow (UPBF)[1] were determined using radioactive microspheres (15±5 μm diameter) labeled with ^{85}Sr, ^{141}Ce, or ^{51}Cr (3M Co., St. Paul, Minn.). A 0.2-ml solution containing approximately 500,000 microspheres was diluted with 10% dextran to a 2.0-ml volume. One-fourth of the volume was retained as a standard, while the remaining 1.5 ml was injected through the left ventricular catheter, followed by rapid irrigation of the catheter with 5 ml of isotonic saline. This injection took less than 20 s. Blood was simultaneously withdrawn from the right femoral artery with a Harvard infusion pump (Harvard Apparatus Co., Inc., Millis, Mass.) at a rate of 5 ml/min for 1 min.

At the completion of the experiments, the uteri and placentas were removed, weighed, and digested in concentrated HCl. In experiments in which renal blood flow was determined, the kidneys were removed and digested. The digested volume was measured, and aliquots were counted with reference femoral samples and the remaining 0.5 ml of the injectate in a Packard autogamma counter (Packard Instrument Co., Inc., Downers Grove, Ill.). ^{85}Sr was counted at the 0.510 MeV peak, ^{141}Ce at the 145 MeV peak, and ^{51}Cr at the 0.310 MeV peak. No correction was necessary for the ^{85}Sr counts, but correction was made for crossovers of ^{85}Sr into ^{141}Ce and ^{51}Cr and similarly for ^{51}Cr and ^{141}Ce. In previous experiments, uterine vein blood was obtained for 1 min after injection of the microspheres and contained no radioactivity above background, indicating the spheres were trapped by the capillary circulation of the uterus.

In all experiments, viability of the fetuses was determined and only those experiments in which most of the fetuses were alive at the completion of the experiment were accepted.

[1] *Abbreviations used in this paper:* CO, cardiac output; MAP, mean arterial pressure; PGE, prostaglandin E; UPBF, uteroplacental blood flow.

Prostaglandin E was measured by radioimmunoassay utilizing a method previously reported (8). The method does not distinguish between prostaglandin PGE_1 and PGE_2 and, thus, all values are expressed as PGE. Cardiac output and organ blood flow were determined by the following calculations: Cardiac output (ml/min)/cpm injected = blood withdrawal rate (ml/min)/total cpm in blood; organ blood flow (ml/min)/total cpm in organ = blood withdrawal rate (ml/min)/total cpm in blood. Uterine vascular resistance was calculated by dividing mean arterial pressure by uterine blood flow and expressed as millimeters of mercury per milliliters per minute. Results are expressed as mean±SEM. Statistical difference was determined by a paired *t* test.

Group I experiments. After blood pressure and pulse had stabilized, microspheres were injected to establish control values (period I). A rise in arterial pressure was induced by ligation of the noncatheterized common carotid artery. After a 15-min waiting period blood samples were collected and a second set of microspheres were injected (period II). Intravenous diazoxide (Hyperstat, Schering Corp., Kenilworth, N. J.), 5–7 mg/kg (eight animals), pentolinium (Ansolysen, Wyeth Labs, Philadelphia, Pa.) 2 mg/kg (two animals), or trimethaphan (Arfonad, Roche Labs., Division of Hoffman-LaRoche, Inc., Nutley, N. J.), in sufficient amount, (four animals), was administered to reduce mean arterial pressure (MAP) by approximately 40 mm Hg. After stabilization, the third set of microspheres was injected (period III). The order of injection of the different isotopically labeled microspheres was varied among animals.

Group II experiments. Six animals were subjected to a protocol similar to group I. A 0.1-mg/kg per min infusion of meclofenamate was given for 20 min. The first set of microspheres was injected and samples collected 30 min after carotid occlusion and diazoxide administration.

Group III experiments. This group of six animals was made hypotensive by intravenous trimethaphan until MAP fell to between 36 and 42 mm Hg. We found that only trimethaphan could uniformly reduce pressure to this level. Initial samples were collected and the first microsphere injection was performed. Samples were collected and a second set of microspheres were injected after the pressure had stabilized at the hypotensive level. In these experiments renal blood flow and UPBF were determined.

RESULTS

Group I. The results of the group I experiments are depicted in Table I and Fig. 1. UPBF remained virtually unchanged at 30±3.2, 27.4±5.2, and 29.3±4.5 ml/min as MAP varied from control levels of 93.1±2.6 to 109±4.1 mm Hg after carotid ligation, and 73.8±1.3 mm Hg after the antihypertensive drug. The range of pressure variation was from 60 to 135 mm Hg in this group of experiments. This constancy of UPBF occurred with a mean change in uterine vascular resistance from 3.7 to 5.4 mm Hg/ml per min after carotid ligation. Although the increase in uterine vascular resistance was not statistically significant during carotid ligation (period II) ($P < 0.1$), the subsequent reduction in resistance following the antihypertensive drug (period III) from 5.4 to 3.2 mm Hg/ml per min was statistically significant ($P < 0.025$). Variability in control UPBF from experiment to experiment was due

TABLE I

Effect of Perfusion Pressure on UPBF

Experiment no.	MAP			CO			UPBF			UPBF			Uterine vascular resistance		
	I*	II‡	III§	I	II	III	I	II	III	I	II	III	I	II	III
	mm Hg			*ml/min*			*% CO*			*ml/min*			*mm Hg/ml/min*		
Normal pregnancy, Group I															
1	98	135	75	599	605	528	5.6	6.8	6.4	33.8	41.2	33.7	2.9	3.3	2.2
2	104	126	75	643	583	705	4.5	3.2	5.6	29.3	18.4	39.3	3.5	6.8	1.9
3	95	111	80	622	637	701	2.5	2.2	1.9	15.6	14.0	13.9	6.1	7.9	5.8
4	95	110	70	795	643	730	3.8	2.7	6.1	30.1	17.3	22.3	3.2	6.4	3.1
5	82	82	68	591	686	604	4.9	4.7	4.9	29.1	32.2	29.7	2.8	2.7	2.3
6	85	100	60	596	376	483	7.0	2.5	4.2	41.8	9.5	20.3	2.0	10.5	3.0
7	92	102	73	435	371	391	2.7	4.5	3.3	11.8	16.5	13.0	7.8	6.2	5.6
8	100	108	78	495	329	439	8.6	10.0	7.7	43.0	34.0	34.0	2.3	3.2	2.3
9	90	105	75	384	481	363	6.1	5.4	5.5	23.4	25.8	20.0	3.9	4.1	3.8
10	85	120	75	582	601	624	9.8	14.0	12.4	57.1	86.0	77.0	1.5	1.4	0.97
11	87	103	75	839	687	675	4.2	5.4	6.2	35.1	37.5	42.1	2.5	2.8	1.8
12	85	100	76	744	579	634	3.8	3.9	5.6	28.0	22.8	35.3	3.0	4.4	2.1
13	87	94	78	696	484	389	3.2	2.7	3.5	22.5	13.1	13.7	3.8	7.2	5.7
14	118	135	75	452	265	294	4.2	6.0	5.4	18.8	15.8	16.0	6.3	8.5	4.7
Mean	93.1	109	73.8	605	523	540	5.6	5.3	5.6	30.0	27.4	29.3	3.7	5.4	3.2
±SEM	2.59	4.05	1.34	35.9	37.3	39.1	0.58	0.87	0.65	3.2	5.2	4.5	0.48	0.71	0.43
P		<0.001	<0.001		NS	NS		NS	NS		NS	NS		NS	0.025
Prostaglandin-inhibited animals, Group II															
1	124	160	120	716	638	826	4.5	4.6	4.0	31.9	29.0	33.0	3.9	5.5	3.6
2	100	106	90	469	320	348	2.8	3.1	3.4	13.1	9.8	11.7	7.6	10.8	7.7
3	94	89	67	354	387	465	5.7	5.0	4.8	20.3	19.5	22.4	4.6	4.6	3.0
4	85	100	80	306	228	234	1.7	1.8	2.3	5.2	4.0	5.4	16.3	2.5	14.8
5	85	125	80	300	249	415	1.7	1.8	1.0	5.1	4.6	4.3	16.7	29.2	18.6
6	108	112	80	400	319	439	2.3	3.4	2.0	9.3	11.0	8.7	11.6	10.2	9.2
Mean	99.3	115.3	89	424	357	454	3.1	3.3	2.9	14.2	13.0	14.3	10.1	14	9.5
±SEM	5.6	9.3	6.7	63.7	60.9	81.7	0.7	0.6	0.6	4.2	3.9	4.6	2.3	4.0	2.5
P		<0.005	<0.05		<0.025	NS		NS	NS		NS	NS		NS	<0.01

* Control period.
‡ Carotid ligation.
§ Antihypertensive drug.

primarily to the difference in size of the uterus and the number of fetuses present.

Group II. The data from animals in the meclofenamate-treated group are depicted in Table I and Fig. 2. Although mean UPBF was lower in the prostaglandin-inhibited animals, the difference was not statistically significant. However, uterine vascular resistance was significantly higher ($P < 0.01$) in these animals than in group I. Constancy of flow was again demonstrated over the range of perfusion pressure from 67 to 160 mm Hg. UPBF was 14.2±4 ml/min or 3.1±0.7% of cardiac output (CO) in the control period, 13±4 ml/min or 3.3 ±0.6% CO postcarotid ligation, and 14.3±5 ml/min or 2.9±0.6% CO after the antihypertensive agent was administered. The fall in uterine vascular resistance from 14 to 9.5 mm Hg/ml per min after diazoxide was significant ($P < 0.01$). Carotid ligation caused a significant decrease in CO in these experiments ($P < 0.025$) but no change in UPBF. Diazoxide administration caused CO to rise to control levels as MAP fell from 115±9.3 to 89±6.7 mm Hg. There was no greater rise in arterial pressure after carotid ligation in the prostaglandin-inhibited animals than in group I animals. PGE concentration from the inferior vena cava was 162±94 ng/ml before meclofenamate. The large variability represents differences in the placement of the catheter, which resulted in greater dilution of the high uterine vein PGE concentration. However, 30 min after meclofenamate, the PGE level fell in each animal with a mean value of 1.48±0.86 ng/ml. Although uterine PGE secretion could not be determined from these experiments, the reduction in inferior vena cava PGE concentration would indicate prostaglandin inhibition had occurred.

Group III. In an attempt to determine the effect of lower perfusion pressure, intravenous Arfonad was given until MAP fell to approximately 40 mm Hg. At this pressure, UPBF fell significantly, both expressed as percentage of CO, 6.1–2.5%, and in absolute values, 32±5-10.6±3 ml/min (Table II and Fig. 3). In all but one experiment, uterine vascular resistance rose with this degree of hypotension and mean uterine vascular resistance rose from 3.7 to 6.2 mm Hg/ml per min ($P < 0.1$). In contrast, renal vascular resistance fell

TABLE II

Effect of Hypotension on Uteroplacental and Renal Blood Flow

Experiment no.	MAP		CO		UPBF		UPBF		Uterine vascular resistance		Renal blood flow		Renal blood flow		Renal vascular resistance	
	C*	E‡	C	E	C	E	C	E	C	E	C	E	C	E	C	E
	mm Hg		*ml/min*		*% CO*		*ml/min*		*mm Hg/ml/min*		*% CO*		*ml/min*		*mm Hg/ml/min*	
1	80	38	510	423	3.0	1.4	15.6	5.9	5.1	6.4	13.8	16.6	70.5	70.4	1.13	0.54
2	95	42	458	467	6.9	1.7	31.8	8.1	3.0	5.2	16.7	9.3	76	43.3	1.25	0.97
3	95	38	582	414	6.5	0.5	38	2.3	2.5	16.5	12.8	16	75	68	1.27	0.56
4	95	42	533	415	7.3	5.3	39	22	5.5	1.9	17.3	13.4	92	56	1.03	0.75
5	94	36	490	421	4.0	1.0	21	7.7	4.3	4.7	22	15	92.2	61	1.02	0.59
6	93	39	511	302	9.0	5.0	49	17.7	1.9	2.2	7	8	40.9	24.4	2.27	1.6
Mean	92	39	514	407	6.1	2.48	32.4	10.6	3.72	6.15	14.9	13	74.5	53.8	1.33	0.84
±SEM	±2.4	±0.98	±17	±22	±0.9	±0.9	±5	±3.1	±0.59	±2.2	±2	±1.5	±7.7	±7.1	±0.19	±0.17
P	<0.001		<0.025		<0.05		<0.025		NS		NS		NS		<0.001	

* Control.

‡ Experimental.

significantly from 1.33 to 0.84 mm Hg/ml per min ($P < 0.001$), as renal blood flow was maintained relatively constant in the face of a significant fall in CO, from 514 to 407 ml/min ($P < 0.025$); and pressure, from 92±2.4 to 39±1 mm Hg ($P < 0.001$).

DISCUSSION

The classic method to determine autoregulation involves either changing perfusion pressure to an isolated organ or, in the intact animal, changing perfusion pressure only to the organ under study. This allows for determination of an isolated response without change in resistance of other vascular beds. From a clinical standpoint, however, one is not concerned with an isolated response but rather the effect of arterial pressure upon flow, while varying resistances are simultaneously occurring in other vascular beds. Thus, the use of carotid ligation to induce hypertension by activation of the sympathetic nervous system, and arteriolar dilation or ganglionic blocking drugs to induce hypotension does not measure autoregulation in the classic sense, but does measure the capacity of the uterine circulation to vary resistance with changes in arterial pressure. The frequent occurrence of hypertension during human pregnancy and the question of the effect of antihypertensive agents on uterine blood flow make such determinations particularly pertinent.

The present studies indicate that over a wide range of perfusion pressure, the uteroplacental circulation of the pregnant rabbit maintains relative constancy of blood flow (Fig. 4). This is in contrast to previous reports in the pregnant ewe in which changes in aortic pressure resulted in linear changes in uterine blood

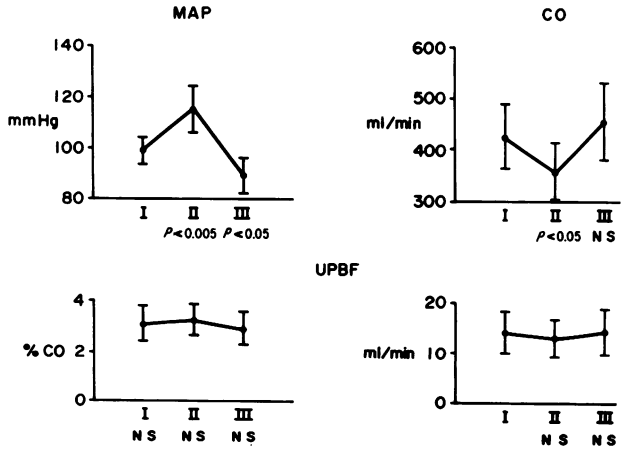

FIGURE 2 The effect of variation in MAP on CO and UPBF in the prostaglandin-inhibited animal.

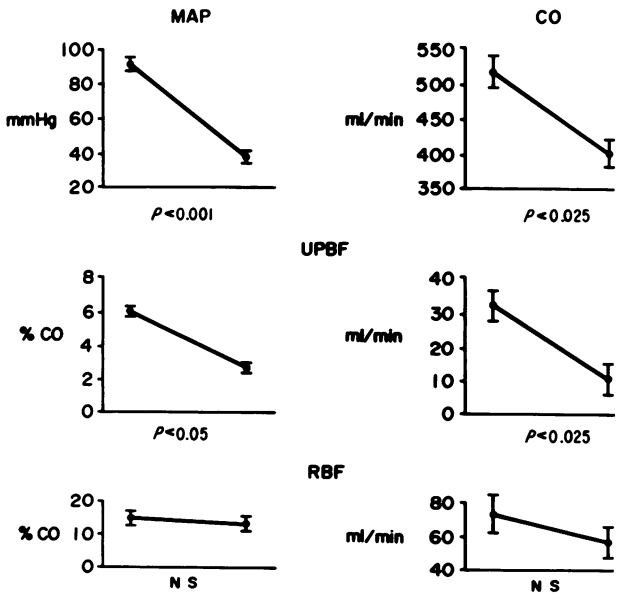

FIGURE 3 The effect of Arfonad-induced hypotension upon MAP, CO, UPBF, and renal blood flow (RBF).

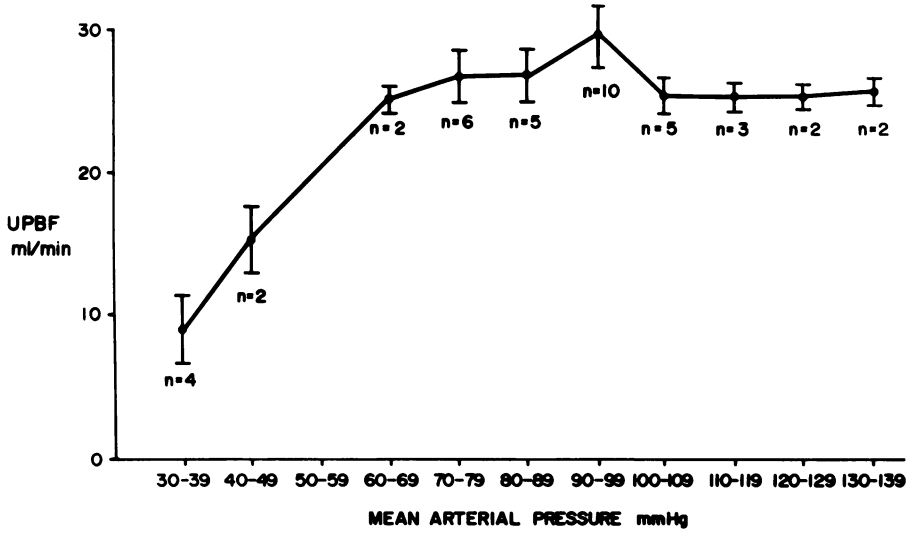

FIGURE 4 Summary of all experiments plotting UPBF against MAP. n = number of animals in each arterial pressure bracket.

flow. The difference in placental implantation and the absence of uterine renin in the ewe may be significant in its response to change in perfusion pressure. Also, when utilizing an electromagnetic flow probe to measure flow in one uterine artery, there is wide variation in control uterine blood flow at similar perfusion pressure, which makes statistical evaluation of the data difficult. In the studies reported by Ladner et al. (1), carotid occlusion caused arterial pressure to rise from 105±4 to 142±7 mm Hg, similar to the rise induced by norepinephrine, from 102±3 to 147±8 mm Hg; uterine blood flow rose from 270±44 to 385±65 ml/min during carotid ligation but only from 306±40 to 345±51 ml/min during norepinephrine. In experiments where angiotensin was infused to raise blood pressure, control uterine blood flow, 442±54 ml/min, was higher than after either carotid ligation or norepinephrine, and rose to 525±54 ml/min with a rise in arterial pressure from 113 to 150 mm Hg. When spinal anesthesia or hydralazine was used to induce hypotension, control uterine blood flow varied from 563±32 ml/min in the anesthesia experiments to 232±27 ml/min in the hydralazine experiments. Although uterine blood flow fell to 188±32 ml/min with spinal anesthesia and to 120±15 ml/min with hydralazine, the perfusion pressure with both maneuvers was 41 mm Hg, which may be below the autoregulatory range, if one does exist in the ewe. Our studies in the rabbit showed UPBF fell sharply when arterial pressure was reduced to 38–42 mm Hg. Thus, the previous studies in the pregnant ewe are not convincing of the inability of the uterine vasculature to vary resistance with change in perfusion pressure.

Since the question has been raised as to whether an ischemic uterine circulation can alter resistance in response to reduction in perfusion pressure, studies of the regulation of UPBF were conducted in the prostaglandin-inhibited animal. We have previously shown that inhibition of prostaglandin synthesis reduced UPBF (8), and the uteroplacental circulation of the pregnant rabbit has a greater PGE secretion than the renal. In spite of the increased uterine vascular resistance caused by prostaglandin inhibition, UPBF remained constant over a range of arterial pressure from 67 to 160 mm Hg with a significant reduction in uterine vascular resistance occurring after use of diazoxide.

It has been reported by Herbaczynska-Cedro and Vane (9) that renal autoregulation in the isolated kidney preparation was dependent upon intrarenal prostaglandin synthesis. However, autoregulation occurs when aortic pressure is lowered in the prostaglandin-inhibited anesthetized dog (10). It appears that in both the kidney and uterus, autoregulation of flow is due to an intrinsic myogenic property of the vasculature not dependent upon PGE synthesis. This may have relevance to human toxemia where there is evidence that a reduction in uteroplacental blood occurs. Uterine hypoperfusion has been used as an argument against the use of antihypertensive therapy because of concern that an ischemic uterine circulation required hypertension for adequate perfusion. If the reduction in UPBF after prostaglandin inhibition has similarities to toxemia, these experiments provide evidence that even with reduced uterine flow and elevated vascular resistance, vasodilatation occurs with reduction in perfusion pressure. The fact that the prostaglandin-inhibited uterus can vary resistance in response to change in perfusion pressure does not mean, however, that uterine PGE is not important in regulating uterine blood flow. Previous

experiments have demonstrated that either indomethacin or meclofenamate reduce UPBF by approximately 50% in the pregnant rabbit (8). Base-line uterine blood flow may be, in part, under the control of PGE, but the myogenic response to changes in perfusion pressure may be independent of PGE. Prostaglandin inhibition may increase uterine vascular resistance by potentiating responsiveness to circulating norepinephrine (11).

The PGE concentration of inferior vena cava blood, sampled from above the uterine veins, was 162±94 ng/ml in five animals which fell to 1.48±0.86 ng/ml after meclofenamate. The wide SE was due to the inability to exactly position the catheter at the uterine vein outflow tract. Previous determinations of directly catheterized uterine vein PGE revealed 172±48 ng/ml before and 23±9.8 ng/min after prostaglandin inhibition (8). High values for uterine vein PGE_2 concentration in the rabbit have also been found recently using gas chromatography and mass spectrometry.[2]

With severe hypotension induced by Arfonad a significant reduction in UPBF occurred, expressed both in absolute values and as a percentage of CO. In contrast, no significant reduction in renal blood flow occurred. We have previously reported that during hemorrhagic hypotension to 72 mm Hg in pregnant rabbits, renal blood flow was 16±3.2% of CO (5), and renal vasodilatation (12) and preservation of renal blood flow during hemorrhagic hypotension have been reported in dogs and primates (13). These studies would indicate that uterine blood flow is not maintained as well as renal blood flow with severe hypotension induced by ganglionic blockade.

Although changes in myometrial contraction could alter uterine vascular resistance, the microsphere method measures instantaneous flow and is not likely to be altered uniformly by uterine contractions. Diazoxide, a smooth muscle relaxant, is known to reduce myometrial contractions but ganglionic blocking drugs have not been demonstrated to have this effect. The anatomical spiraling of the uterine arteries as they traverse the myometrium is thought to prevent constriction of the vessels as the myometrium contracts. The change in uterine vascular resistance produced by uterine nerve stimulation can be separated from the effect of compression by myometrial contraction (14).

Since pregnancy is frequently associated with hypertension, the effect of arterial pressure upon uterine blood flow has important clinical implications. Concern about treating the hypertension associated with toxemia has been related to the view that hypertension increased uterine blood flow. Also, the transplacental transfer of oxygen is a flow-dependent process (15) and dependence of uterine blood flow on arterial pressure would place the fetus in jeopardy with reduction in arterial pressure. However, the human uterus contains a rich autonomic innervation (16) and pharmacological studies have demonstrated the presence of both alpha and beta receptors. Isoproterenol increases UPBF in the pregnant rabbit (5), and stimulation of the uterine nerve in the pregnant dog causes uterine vasodilatation (14). Thus, the uterine vasculature does not lack the neurogenic capacity to vary vascular resistance.

If the uterus lacked the capacity to alter vascular resistance, hypertension should increase uterine blood flow. The recent findings of Brinkman et al. (17), that UPBF falls in the pregnant ewe after hypertension induced by renal artery stenosis, and the studies we report in the pregnant rabbit, argue against the inability of the uterine vasculature to alter resistance in response to pressure.

[2] Frölich, J. C. Personal communication.

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