Anesthesiology
54:131–135, 1981

Epinephrine Does Not Alter Human Intervillous Blood Flow during Epidural Anesthesia

George A. Albright, M.D., Riitta Jouppila, M.D.,† Arno I. Hollmén, M.D.,‡ Pentti Jouppila, M.D.,§ Hannu Vierola, M.D.,¶ Antero Koivula, M.S.***

The effect of epinephrine given epidurally with local anesthetics on uterine blood flow is controversial. Previous work in pregnant ewes demonstrated a transient but significant (14 per cent) decrease in uterine blood flow when 2-chloroprocaine with epinephrine (10 μg/ml) was used. The authors administered 2-chloroprocaine, 10 ml, with epinephrine (5 μg/ml) to 12 healthy women during the first stage of labor. By use of intravenously injected ^{133}Xe, intervillous blood flow was measured before and 15–20 min after epidural anesthesia to a somatic level of at least T10. Intervillous blood flow did not change significantly despite a decrease in mean blood pressure of 11 torr. These conflicting results are probably best explained by methodologic and species differences. It is postulated that human placental vasculature, unlike that of the ewe, undergoes vasodilatation when perfusion pressure is decreased to maintain placental blood flow. (Key words: Anesthesia, obstetric. Anesthetic techniques, epidural. Measurement techniques: intervillous blood flow. Placenta: blood flow. Sympathetic nervous system, catecholamines: epinephrine.)

THE ADDITION OF epinephrine to local anesthetic solutions for epidural anesthesia in obstetrics remains controversial. Epinephrine (5 μg/ml) has been demonstrated to decrease vascular absorption of local anesthetic agents and to improve the quality, intensity, and duration of the block. However, there is uncertainty concerning the effect of absorbed epinephrine from the epidural space on uterine activity and, more importantly, on uterine blood flow (UBF).

Epinephrine infused into the pregnant ewe causes a marked decrease in UBF and a marked increase in skeletal muscle blood flow.[1] In normotensive pregnant ewes, Wallis *et al.*[2] demonstrated a transient 14 per cent decrease in UBF shortly after the onset of epidural anesthesia with 2-chloroprocaine containing epinephrine, whereas uterine blood flow did not change in ewes receiving 2-chloroprocaine only. These investigators postulated that the uterine vasculature of the pregnant ewe may undergo alpha-adrenergic vasoconstriction as a result of the effects of low concentrations of epinephrine, while the vasculatures of other tissues (skeletal muscle, spleen and fat) undergo beta-adrenergic vasodilatation, thereby directing blood flow away from the uterus.

Direct calculation of intervillous blood flow (IBF) from the clearance of intravenously injected ^{133}Xe is feasible for a pregnant woman who has an anterior placenta.[3] Using the ^{133}Xe technique, Jouppila *et al.*[4] found no significant change in IBF with lumbar epidural anesthesia for elective cesarean section in nine patients when 16–20 ml of 1.5 per cent lidocaine with epinephrine (5 μg/ml) was used. Similarly, the administration of epidural anesthesia with bupivacaine, 4 ml, with and without epinephrine (20 μg) for relief of labor pain had no deleterious effect on IBF.[5] This study evaluates the effects of a larger amount of epinephrine (50 μg) on IBF during epidural anesthesia with 2-chloroprocaine, 10 ml, for the first stage of labor.

Materials and Methods

Twelve healthy mothers in labor desiring epidural anesthesia, whose normal pregnancies (without signs of uteroplacental insufficiency) ended in vaginal delivery of normal infants in the 37th to 42nd weeks of gestation, were studied (table 1).

The placenta was located by ultrasonic B scanning. Only patients in whom the placenta was on the anterior wall of the uterus, and who provided informed consent, were included in the study. The protocol for this study was approved by the Oulu University Ethical Committee on the use of Human Subjects in Research. Labor was induced electively by oxytocin infusion in all but two patients, who had spontaneous labor. The membranes were artificially ruptured when labor was established (as evidenced by cervical change) and direct monitoring of fetal heart rate†† and intrauter-

* Associate Professor of Clinical Anesthesia, Stanford University Medical School, Stanford, California 94305.

† Senior Anesthetist, Department of Anesthesia, Oulu University.

‡ Professor and Chairman, Department of Anesthesia, Oulu University.

§ Senior Obstetrician, Department of Obstetrics and Gynecology, Oulu University.

¶ Resident Obstetrician, Department of Obstetrics and Gynecology, Oulu University.

** Master of Science, Department of Clinical Chemistry, Oulu University.

Received from the University of Oulu, Central Hospital, Oulu, Finland. Accepted for publication July 31, 1980. Presented at the joint Obstetric Anaesthetists Association (OAA) and Society for Obstetrics, Anesthesia and Perinatology (SOAP) meeting, Birmingham, England, September 1979.

Address reprint requests to Dr. Albright: Department of Anesthesia, Stanford University Medical Center, Stanford, California 94305.

†† Hewlett-Packard 8030A cardiotocograph, Hewlett-Packard, Palo Alto, California 94304.

0003-3022/81/0200/0131 $00.75

TABLE 1. Demographic Data of 12 Mothers Given Epidural Anesthesia with 2-Chloroprocaine with Epinephrine (5 μg/ml)

	Mean ± SD	Range
Age (years)	25 ± 4	20–33
Parity	1.3 ± 0.7	1–3
Gestation (weeks)	41 ± 1	37–42
Apgar score		
1 min	9 ± 0.3	8–9
5 min	9 ± 0.5	9–10
Birth weight (g)	3,503 ± 357	2,760–4,030

ine pressure‡‡ were instituted. These variables were monitored and the oxytocin infusion was maintained at a constant rate (mean 11 ± 5.4 mU/min) for at least 30 min before and during the measurements of intravenous ^{133}Xe.

Epidural anesthesia was provided for pain relief during the first stage of labor when the cervix was dilated 3–5 cm (mean 3.9). An epidural catheter was inserted 1–2 cm into the epidural space through a needle positioned at L2–3 or L3–4. The patients were lying in a 15° left lateral position and had systolic and diastolic blood pressure values measured every 3 min throughout the study period. After the first measurement of intravenous ^{133}Xe, 2-chloroprocaine, 10 ml, with epinephrine (5 μg/ml) was injected slowly between uterine contractions (3-ml test dose followed in 5 min with 7 ml). The patients received a minimum of 500 ml of lactated Ringer's solution rapidly to maintain systolic blood pressure at or above 100 torr. The IBF was measured again 15–20 min after the onset of anesthesia. Measurement was commenced immediately after cessation of a uterine contraction, as determined from the intrauterine pressure tracing.

The intravenous ^{133}Xe technique for measurement of IBF has been described in detail by Rekonen *et al.*[3] In brief, approximately 2 mCi of ^{133}Xe are injected rapidly and flushed with saline solution, 10 ml, into an antecubital vein while the patient holds her breath for about 15–20 s to diminish the escape of ^{133}Xe through the lungs. The radioisotope enters the systemic circulation and reaches the uterus and placenta, where its clearance is measured for 5–10 min with a scintillation detector positioned over the abdomen, above the center of the placenta. The diameter of the area at the level of the placenta used for measurement is about 10 cm. A biexponential clearance curve

$$A_1e^{-1k_1t} + A_2e^{-1k_2t}$$

is obtained, in which the shorter half-life component (0.56 ± 0.16 min) reflects blood flow in the intervillous space and the longer component (6.7 ± 3.0 min), myometrial blood flow. The IBF is obtained from the equation $F_1 = 100 \cdot k_1$. The myometrial blood flow is calculated from the equation $F_2 = \lambda \cdot k_2$, where λ is the partition coefficient of xenon between blood and myometrial tissue (70/100 g). The separation of the intervillous component from the slower myometrial component is readily accomplished, since the peak activity (500–1,000 counts/5 s) in the placental component is about three times higher than that of the myometrial component. The radioisotope reaching the placenta is not an impulse function but has an exponentially descending tail with a half-life of about 3 s. This has no significant effect on the intervillous removal curve, which usually has a half-time longer than 20 s. Diffusion of xenon from the intervillous blood pool into the fetal circulation is slow and does not appreciably influence the results, as demonstrated by Lippert *et al.*[6] using consecutive injections of diffusible ^{133}Xe and nondiffusible ^{99m}Tc-albumin. The dose of radiation to the mother and fetus is less than 1 mrad, which is only a tenth of the dose of radiation associated with conventional placental scanning, or one-hundredth the radiation dosage from annual background radiation or radiographic pelvimetry (80–100 mrad).

The mean ± SD IBF in normal pregnancy is 135 ± 49 $ml \cdot 100\ g^{-1} \cdot min^{-1}$.[3] Reproducibility of the method was ±20 $ml \cdot 100\ g^{-1} \cdot min^{-1}$, with a regression coefficient of 0.88 when two measurements were made about 30 min apart in 24 patients.[4] This variation is not surprising, considering that the method does not measure total IBF but only the flow per unit volume over the central area of the placenta. Slight axial rotation of the uterus may alter the area of the placenta being measured, thereby introducing errors, since IBF is not uniform throughout the placenta.[7] Abdominal wall clearance of ^{133}Xe is slow (adipose tissue half-life = 230 min,[10] λ = 1,000/100 g) and slight,[8–10]§§ without appreciable effect on IBF values, but may result in lower myometrial blood flow values.[3] The inhalational ^{133}Xe technique requires correction for recirculation,[11,12] but recirculation is not a significant factor in the intravenous ^{133}Xe technique (fig. 1).

Measured values were compared statistically using Student's *t* test for paired data. $P < 0.05$ was regarded as significant.

Results

Intervillous blood flow increased in seven patients (30–255 per cent), was unchanged in two patients

‡‡ Hewlett-Packard 1280B/C physiological pressure transducer and 15137A transducer adapter.

§§ Skin, subcutaneous, and skeletal muscle tissue blood flows in nonpregnant subjects are 5.7 ± 1.3, 2.6 ± 1.7, and 2.5 ± 1.4 $ml \cdot 100\ g^{-1} \cdot min^{-1}$, respectively.

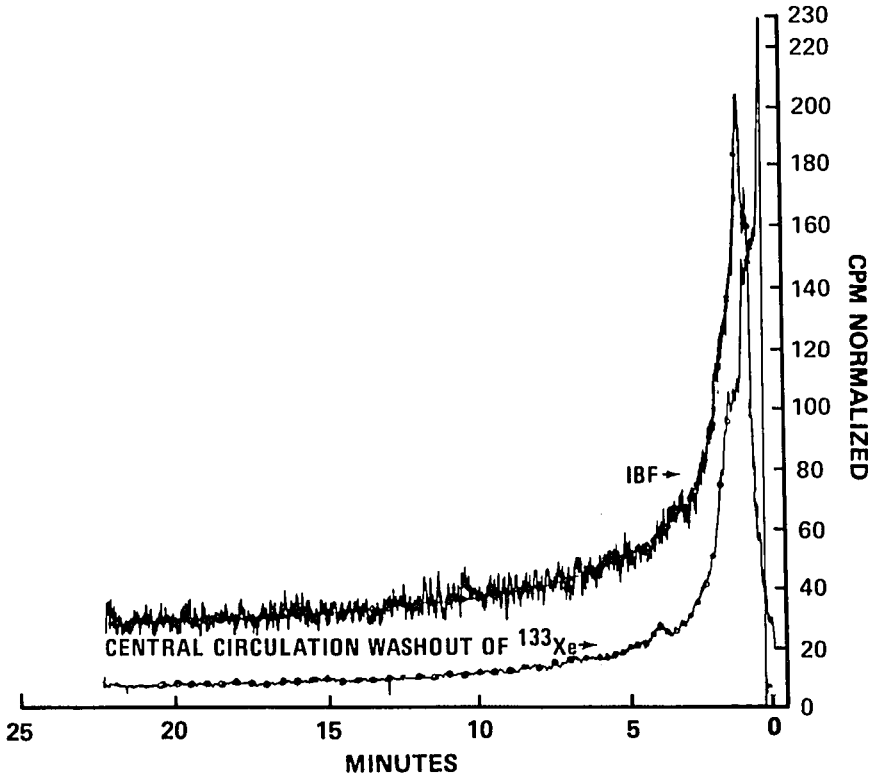

FIG. 1. ^{133}Xe clearance curves with scintillation detectors positioned over the placenta (IBF) and heart (central circulation), indicating no upslope for the central circulation curve, consistent with lack of reentry or recirculation of the radionuclide.

(0–3 per cent), and decreased in three patients (21–59 per cent) after epidural anesthesia with 2-chloroprocaine with epinephrine (table 2). These changes were not statistically significant.

All patients had systolic blood pressures at or above 100 torr during each IBF measurement (table 2). Mean blood pressure was calculated from systolic and diastolic blood pressures (mBP = DBP + ⅓ pulse pressure). The mean blood pressure of 94 ± 8 torr and the diastolic blood pressure of 76 ± 7 torr before anesthesia decreased to 83 ± 10 and 63 ± 10 torr, respectively. These values are significantly different ($P < 0.01$). Two (Patients 2 and 11) of the three patients who had decreases in IBF had mean blood pres-

TABLE 2. Intervillous Blood Flow (IBF) and Arterial Pressure (BP) before and after Epidural Anesthesia with 2-Chloroprocaine with Epinephrine, 5 μg/ml

	IBF (ml·100 g^{-1}·min^{-1})			BP (torr)			
				Before		After	
	Before	After	Per Cent Change	Systolic/ Diastolic	Mean	Systolic/ Diastolic	Mean
Patient 1	269	380	+41	126/82	97	130/55	80
Patient 2	197	137	−30	115/70	85	100/45	63
Patient 3	241	428	+78	125/78	94	120/60	80
Patient 4	94	232	+146	138/78	98	140/80	100
Patient 5	138	138	0	140/85	103	110/70	83
Patient 6	311	129	−58	140/80	100	136/60	85
Patient 7	366	474	+30	130/80	97	120/70	87
Patient 8	103	366	+255	130/70	90	115/60	78
Patient 9	110	182	+65	135/80	98	110/60	77
Patient 10	99	103	+3	140/75	97	135/75	95
Patient 11	247	195	−21	105/60	75	105/55	72
Patient 12	230	452	+97	130/70	90	140/70	93
MEAN	200	268	+50	130/76*	94*	122/63*	83*
SD	±92	±141	±87	±11/±7	±8	±14/±10	±10

* $P < 0.01$.

TABLE 3. Uterine Activity

	Montevideo Units		Intrauterine Tone (torr)	
	Before	After	Before	After
Patient 1	205	140	25	20
Patient 2	66	45	10	10
Patient 3	70	35	35	25
Patient 4	100	90	40	65
Patient 5	100	125	35	35
Patient 6	155	180	35	35
Patient 7	195	125	15	10
Patient 8	105	50	15	15
Patient 9	50	40	30	25
Patient 10	125	75	30	35
Patient 11	170	160	40	35
Patient 12	45	45	15	10
MEAN	115	93	27	27
SD	±55	±52	±11	±16

sures of less than 75 torr at the time of the second IBF measurements even though systolic blood pressures were 100 torr or higher. The third (Patient 6) had an adequate blood pressure, but a strong uterine contraction immediately after the start of the second IBF measurement may have interfered with the accuracy of its measurement.

Uterine activity (table 3), as measured in Montevideo units,¶¶ did not significantly change after anesthesia. Values of resting uterine tone before and after anesthesia did not differ significantly. Higher than anticipated values for resting uterine tone, observed in the majority of our patients, were probably the result of inappropriate zeroing of the pressure-monitoring system. These patients did not have obstetric complications associated with increases in baseline uterine tone; the rate of oxytocin infusion was low, and uterine activity, as measured by Montevideo units, was not excessive.

Relief of labor pain was good or excellent in every patient. The fetal heart rates were normal in all fetuses except that of Patient 5, in which variable decelerations occurred during the end of the second IBF measurement. Subsequently, there was fetal tachycardia with intermittent late decelerations. Measured fetal scalp blood *p*H was 7.33. Three hours later, Patient 5 delivered a healthy infant with Apgar scores of 9–9.

Discussion

The mean IBF in our study group was higher than the values for near-term, non-laboring patients reported by Rekonen *et al.*[3] and by Husemeyer and Crowley.[11] The higher IBF values for laboring patients in this study are consistent with the hypothesis of "reactive hyperemia" following a uterine contraction, as demonstrated by Lees *et al.*[13] in the term rhesus monkey.

Lumbar epidural anesthesia during the first stage of labor with 2-chloroprocaine with epinephrine (50 μg) did not cause any significant change in IBF. The principal reasons for divergent results between our study and that by Wallis *et al.* are probably related to methodologic and species differences. In the Wallis study,[2] the ewes were highly instrumented, not in labor, had a 2,000-ml fluid load to maintain normotension, and were exposed to a larger dose of epinephrine (60–80 μg) at a stronger concentration (10 μg/ml). Uterine blood flow, not maternal placental blood flow, was estimated in the ewe using an electromagnetic flow probe secured to a branch of the uterine artery. Using radioactive microspheres, Harbert *et al.*[14] made 45 determinations of uterine blood flow distribution in ten pregnant rhesus monkeys. They found that measurements of uterine-artery blood flow by use of an electromagnetic flow probe on a single uterine artery gave qualitative but not quantitative information about the flow changes in the entire uterine vascular bed. Furthermore, Harbert *et al.*[14] found a fairly constant placental perfusion in spite of circadian variation in total uterine blood flow. Wallis *et al.*[2] utilized radioactive microspheres to demonstrate that the percentage of uterine blood flow distributed to the placenta (84 per cent) was unchanged by epidural anesthesia with and without epinephrine in two ewes, but they did not study the distribution of flow when uterine blood flow was decreased. Therefore, the transient decrease in uterine blood flow observed in the ewes receiving 2-chloroprocaine with epinephrine may have reflected, in part, a decrease in myoendometrial blood flow.

Uteroplacental vasculature has been considered to be widely dilated at rest, capable of vasoconstriction but not further vasodilatation. This conclusion has been drawn mainly from studies of UBF in sheep. Greiss[15] demonstrated that UBF in the pregnant ewe was directly proportional to perfusion pressure without any apparent autoregulation, and more recently, that myometrial blood vessels react well to alpha- and beta-adrenergic stimulation, whereas the placental vessels are largely insensitive to these stimuli.[16] Uterine blood flow distribution in the primate uterus, however, is modulated by factors in addition to physiologic pressure–flow relationships.[14] Radioangiography has demonstrated an acceleration of intervillous perfusion during metaproterenol infusion due to placental vasodilatation in pregnant rhesus monkeys.[17] Results

¶¶ Uterine contraction intensity (torr) times frequency of contractions over a 10-min period.

of radioisotope clearance studies using indium-113m to measure the effect of a beta-mimetic drug, fenoterol, on UBF suggest that human uteroplacental arteries are indeed sensitive to beta-adrenergic stimulation.[18]

Intervillous blood flow was maintained in this study in spite of a significant decrease in mean blood pressure (MBP) after epidural anesthesia. A decrease in perfusion pressure will not affect IBF if there is a corresponding decrease in extrinsic vascular resistance (resting uterine tone or uterine contraction) or a decrease in intrinsic vascular resistance (placental vasodilatation). Since there was no difference between values of resting uterine tone before and after anesthesia and IBF measurements were initiated immediately after the cessation of a uterine contraction, it may be postulated that IBF was maintained because of placental vasodilatation that decreased uterine vascular resistance.

The postulated decrease in placental vascular resistance may be due to beta-adrenergic vasodilatation resulting from the systemic absorption of epidural epinephrine or a decrease in alpha-adrenergic vasoconstriction from sympathetic blockade with a decrease in endogenous catecholamine release secondary to relief of labor pain, or both. Plasma catecholamines were not measured in this study; however, significant increases in plasma epinephrine and norepinephrine values were demonstrated during labor with epinephrine levels below the mean for the group in six of eight patients who received regional anesthesia.[19] The results of this study, coupled with the previous work by Jouppila *et al.*,[4,5] indicate that epinephrine (5 μg/ml) in dosages of 40 to 100 μg, added to local anesthetic solutions, properly placed in the epidural space, has no deleterious effect on IBF so long as significant hypotension is avoided. It is postulated that human placental vasculature, unlike that of the ewe, undergoes vasodilatation when perfusion pressure is decreased.

References

1. Rosenfeld CR, Barton MD, Meschia G: Effects of epinephrine on distribution of blood flow in the pregnant ewe. Am J Obstet Gynecol 124:156–163, 1976
2. Wallis KL, Shnider SM, Hicks JS, et al: Epidural anesthesia in the normotensive pregnant ewe: effects on uterine blood flow and fetal acid–base status. ANESTHESIOLOGY 44:481–487, 1976
3. Rekonen A, Luotola H, Pitkänen M, et al: Measurement of intervillous and myometrial blood flow by an intravenous ^{133}xenon method. Br J Obstet Gynaecol 83:723–728, 1976
4. Jouppila R, Jouppila P, Kuikka J, et al: Placental blood flow during caesarean section under lumbar extradural analgesia. Br J Anaesth 50:275–278, 1978
5. Jouppila R, Jouppila P, Hollmén A, et al: Effect of segmental extradural analgesia on placental blood flow during normal labour. Br J Anaesth 50:563–567, 1978
6. Lippert TH, Fridrich R, Hindemann P, et al: Critical assessment of the xenon washout technic for measurement of placental blood flow. Gynecol Invest 4:14–23, 1973
7. Kuikka J, Käär K, Jouppila P, et al: An intravenous ^{133}Xe method for measuring distribution of placental blood flow. Acta Obstet Gynecol Scand 57:249–251, 1978
8. Sejrsen P: Blood flow in cutaneous tissue in man studied by washout of radioactive xenon. Circ Res 25:215–229, 1969
9. Larsen OA, Lassen NA, Quaade F: Blood flow through human adipose tissue determined with radioactive xenon. Acta Physiol Scand 66:337–345, 1966
10. Lassen NA: Muscle blood flow in normal man and in patients with intermittent claudication evaluated by simultaneous Xe^{133} and Na^{24} clearances. J Clin Invest 43:1805–1812, 1964
11. Husemeyer RP, Crawley JCW: Placental intervillous blood flow measured by inhaled ^{133}Xe clearance in relation to induction of epidural analgesia. Br J Obstet Gynaecol 86:426–431, 1979
12. Jacoby HE, Arnot RN, Glass HI, et al: Estimation of clearance rate of inhaled xenon-133 in the placental region of the pregnant uterus. J Obstet Gynaecol Br Commonw 79:531–537, 1972
13. Lees M, Hill JD, Oghsner AJ III, et al: Maternal placental and myometrial blood flow of the rhesus monkey during uterine contractions. Am J Obstet Gynecol 110:68–81, 1971
14. Harbert GM Jr, Croft BY, Spisso KR: Effects of biorhythms on blood flow distribution in the pregnant uterus (*Macaca mulatta*). Am J Obstet Gynecol 135:828–842, 1979
15. Greiss FC Jr: Pressure–flow relationship in the gravid uterine vascular bed. Am J Obstet Gynecol 96:41–46, 1966
16. Greiss FC Jr: Differential reactivity of the myoendometrial and placental vasculatures: adrenergic responses. Am J Obstet Gynecol 112:20–30, 1972
17. Wallenburg HCS, Mazer J, Hutchinson DL: Effects of a beta-adrenergic agent (metaproterenol) on uteroplacental circulation. Am J Obstet Gynecol 117:1067–1075, 1973
18. Lippert TH, De Grandi PB, Fridrich R: Actions of the uterine relaxant, fenoterol, on uteroplacental hemodynamics in human subjects. Am J Obstet Gynecol 125:1093–1098, 1976
19. Lederman RP, McCann DS, Work B Jr, et al: Endogenous plasma epinephrine and norepinephrine in the last-trimester pregnancy and labor. Am J Obstet Gynecol 129:5–8, 1977