Absence of fetal placental waterfall phenomenon in chronically prepared fetal lambs

KENT L. THORNBURG, JOHN M. BISSONNETTE, AND J. JOB FABER

Departments of Physiology and Obstetrics and Gynecology, School of Medicine, University of Oregon Health Sciences Center, Portland, Oregon 97201

RECENT STUDIES from two laboratories show that the driving pressure of fetal placental blood flow is not the difference between the blood pressure in the fetal umbilical arteries and veins, but the difference between arterial blood pressure and a placental "surrounding pressure" of about 15 mmHg (2, 10, 11). It was further shown (2, 11) that the surrounding pressure could be elevated from its normal value by an increase in maternal uterine vein pressure. This suggested that the "maternal vascular pressure in the placenta directly affects fetal placental blood flow with sluice flow characteristics" (11).

A surrounding (sluice) pressure of 15 mmHg is so high in comparison to a fetal central venous pressure of about 2 mmHg (6), an umbilical vein pressure of 7 mmHg (present series), and a fetal arterial blood pressure of about 40 mmHg (6) that it must be considered a major determinant of fetal placental blood flow in the lamb.

We report here a series of experiments designed to determine whether similar surrounding pressures are demonstrable in the intact fetal umbilical circulation with the ewe unaffected by anesthesia and in a standing position.

METHODS

Pregnant ewes of a variety of Western breeds were anesthetized with halothane in a gas mixture of one-third oxygen and two-thirds nitrous oxide, administered by face mask and continued by endotracheal tube until the end of surgery.

Surgery was performed as previously described (5-7) with minor modifications. An electromagnetic flow sensor of an Omnicraft Mediflow flowmeter was placed on the fetal aorta, distal to the renal arteries. Figure 1 shows a schematic of the complete preparation. In most animals a fetal femoral artery and vein were catheterized with vinyl tubing (Bolab, Derry, N.Y.) and ligated. The tip of the arterial catheter did not reach the flow sensor. The tip of the venous catheter was advanced into the fetal inferior caval vein. Usually the contralateral femoral vessels were also ligated. An inflatable occluder was tied around the umbilical cord where the cord emerged from the abdomen of the fetus. In some experiments, commercially obtained occluders were used, but these often leaked or burst, perhaps being damaged by autoclaving. Disposable occluders manufactured in our laboratory from thin rubber hose and penrose tubing were used in the remaining experiments, but most of these were not capable of occluding the umbilical arteries; all intact occluders permitted the gradual obstruction of umbilical venous flow. The inflation pressure required for partial occlusion of the cord veins was, however, much less than the pressure required for arterial occlusion. RESULTS show that the umbilical artery pressures, downstream from the occluder, did not decrease during partial venous occlusion. An intrauterine catheter for the measurement of uterine pressure was attached to the fetal skin before the fetus was returned to the uterus which was subsequently closed. Distal umbilical arterial and venous branches were catheterized through a new incision (8). The tip of the arterial catheter was advanced a few centimeters toward the cord, and the tip of the venous catheter was advanced...
into a major umbilical vein but distal to the occluder.

A uterine vein was approached through a superficial incision in the uterus, and a catheter was advanced until its tip was in a major trunk of the uterine vein. In the early ewes in the series, we placed an inflatable balloon in the distal caval vein for the purpose of raising uterine vein pressure (2, 11), but we found that the ewes collapsed before a significant rise occurred in the pressure of the uterine vein, perhaps due to the sequestration of large volumes of blood behind the balloon. A greatly enlarged version of the cord occluder was therefore built and secured around the vagina of subsequent ewes. All uterine veins passed through this occluder and uterine vein pressure could be raised by inflation of the occluder without the occurrence of other detectable cardiovascular changes in the ewes (see results). Catheters, tubing, and cable were led to the flank of the ewe through a tunnel underneath her skin and kept in a pouch of surgical tape attached to her flank. Catheters were filled with saline-heparin (about 200 U/ml) and flushed every 48 h.

Finally, catheters were placed in a carotid artery and a jugular vein of the ewe. A single dose of penicillin-G of 1 million units was administered into the amniotic cavity at the end of the surgical procedure. Typical duration of the anesthesia was 4–5 h of which 75 min were spent in cleaning and draping of the animal. Recovery from anesthesia rarely exceeded 10 min.

Fetal blood pressures were recorded with Statham series BB gauges and a Grass P7 polygraph. These were calibrated before every experiment to an accuracy of 0.5 mmHg against a water manometer. Zero base lines were frequently verified during the experiments to eliminate the effects of amplifier drift. Intrauterine pressure was subtracted from all other pressures, as before (6), and intrauterine pressure itself was referred to atmospheric pressure at miduterine level.

The flow sensors were calibrated on excised vessels of appropriate diameter with the use of a Harvard model 1405 pulsatile flow pump by timed collections of sheep blood into a graduate cylinder. The sensors were calibrated at flows encompassing the entire range of flows encountered with the particular sensors in vivo to standard errors of less than 2% of the calibration factors themselves. The automatic nonocclusive zero of the flowmeter sensor combinations were found to be accurate to within 2% of full-scale deflection on the potentiometric Leeds & Northrup speedomax recorder. In addition to the Lceds & Northrup recording, flow was also inscribed on a channel of the Grass P7 polygraph.

Microspheres of 50 μm diam, labeled with niobium-95 or cerium 141, were injected into the femoral vein catheter during a control period for the determination of the nonplacental flow fraction of distal aortic flow. All fetuses were dissected at postmortem to verify the position of the catheters, the occluders, and the flow sensor. The fetuses were divided at the level of the flow sensor heads. The portion of the fetus distal to the flow sensor and the placenta were separately incinerated, and three aliquots of less than 1 ml volume of the blended ashes were counted in a Packard Tri-Carb scintillation spectrometer with appropriate correction for background. About 2,000 spheres were present in the aliquots, which yielded similar isotope concentrations.

RESULTS

Of the 13 animals that survived the operation, one did not have a patent umbilical vein catheter. One other fetus had a resting umbilical vein pressure of 20 mmHg because the umbilical occluder had been tied too tightly around its cord. Since "small" rises in umbilical vein pressure are necessary to demonstrate the presence of a surrounding pressure, we judged that occlusion experiments on this animal would not be meaningful. Eleven animals were, therefore, used for the experiments reported here.

With one exception, 3 days or more were allowed after surgery before the operated fetuses were used for study. The exception was a large fetus (4.7 kg at delivery) who was feared to be due for delivery and was used for study the day after surgery. It was not delivered for 3 days, however, and on the 3rd postoperative day microspheres were injected after which the ewe and fetus were killed for isotope analysis.

Control pH values from fetal femoral artery blood are listed in Table 1. In seven fetuses, femoral blood Po2 was measured also. Fetal placental blood flows, corrected for the fractions of distal aortic blood flows not perfusing the placenta, are listed in Table 1. Mean fetal arterial blood pressure during the control period was 39 mmHg (SEM 3 mmHg), and mean umbilical vein pressure was 7.4 mmHg (SEM 1 mmHg).

None of the animals died during or immediately after the occlusion experiments, and most animals were used at a later time for osmotic experiments unrelated to the present study and then killed.

Correction for nonplacental fraction of distal aortic flow. The distal aorta is a surgically convenient site for the measurement of umbilical blood flow but not a perfect one, since some 9 (9–15%) (5) of the flow at this site does not enter the umbilical arteries (Fig. 1). The fraction depends on the completeness with which the nonumbilical branches of the distal aorta are ligated. The femoral vessels were not ligated in all preparations because of the length of the surgical procedure (Table 1). Perhaps for this reason, the nonplacental fraction of the distal aortic flow was greater than that reported previously, being 21.9% (+ 1.6% SEM) in the 9 of the 11 fetuses in whom microsphere injections were made. One fetus succumbed after the experiment before the microspheres were injected during an attempt to reinsert a catheter under anesthesia (the only case attempted), and a value of 22% was assumed. The other fetuses belonged to a group of five in whom the cord occluder could be inflated sufficiently to completely and acutely interrupt both arterial and venous flows in the cord (e.g., Fig. 2). The nonplacental fraction of the flow that remained after cord occlusion was 20.6% (+ 2.5% SEM) of the control flow in these five fetuses, and not statistically significantly different from the fraction recorded by microsphere injection by either the paired- or unpaired-t test (Table 1). Fetal femoral artery pressure recorded in one fetus during complete cord occlusion
TABLE 1. Control values in 11 experimental fetuses and number and ranges of observations

<table>
<thead>
<tr>
<th>Fetus</th>
<th>Wt, kg</th>
<th>Fraction of distal aortic flow at sensor level that flows through the umbilical vessels; the numbers signify the number of femoral arteries ligated at surgery and the placental flow fractions determined by microspheres and cord occlusion, respectively.</th>
<th>Po, mmHg</th>
<th>pH</th>
<th>qP carried on maternal side</th>
<th>qP on fetal side</th>
<th>Range of Observed Pressures*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.16</td>
<td>2/83/85</td>
<td>18</td>
<td>7.39</td>
<td>163</td>
<td>11-31</td>
<td>1-6.5, 31</td>
</tr>
<tr>
<td>2</td>
<td>2.33</td>
<td>2/78/83</td>
<td>22</td>
<td>7.34</td>
<td>238</td>
<td>11-31</td>
<td>0-7.5, 64</td>
</tr>
<tr>
<td>3</td>
<td>1.96</td>
<td>2/82/NR</td>
<td>NR</td>
<td>7.33</td>
<td>237</td>
<td>11-31</td>
<td>2-9, 60</td>
</tr>
<tr>
<td>4</td>
<td>2.99</td>
<td>2/NR/81</td>
<td>NR</td>
<td>7.40</td>
<td>181</td>
<td>11-31</td>
<td>1.5-8, 117</td>
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<tr>
<td>5</td>
<td>2.79</td>
<td>0/73/71</td>
<td>15</td>
<td>7.39</td>
<td>259</td>
<td>11-31</td>
<td>4-42.5, 58</td>
</tr>
<tr>
<td>6</td>
<td>2.84</td>
<td>1/NR/NR</td>
<td>NR</td>
<td>7.39</td>
<td>182</td>
<td>11-31</td>
<td>5-41, 52</td>
</tr>
<tr>
<td>7</td>
<td>4.67</td>
<td>0/71/71</td>
<td>NR</td>
<td>7.39</td>
<td>183</td>
<td>11-31</td>
<td>5-10, 52</td>
</tr>
<tr>
<td>8</td>
<td>4.13</td>
<td>1/72/NR</td>
<td>21</td>
<td>7.35</td>
<td>185</td>
<td>11-31</td>
<td>2.5-10.5, 71</td>
</tr>
<tr>
<td>9</td>
<td>3.98</td>
<td>2/84/NR</td>
<td>18</td>
<td>7.35</td>
<td>188</td>
<td>11-31</td>
<td>4.5-7.5, 197</td>
</tr>
<tr>
<td>10</td>
<td>3.37</td>
<td>0/80/77</td>
<td>15</td>
<td>7.31</td>
<td>219</td>
<td>11-31</td>
<td>5-35.5, 42</td>
</tr>
<tr>
<td>11</td>
<td>2.52</td>
<td>0/80/77</td>
<td>17</td>
<td>7.35</td>
<td>179</td>
<td>11-31</td>
<td>6-36.5, 27</td>
</tr>
</tbody>
</table>

Mean 3.06 78.1/79.4 19 7.372 186 11-31 1-6.5, 31
SD 0.87 4.9/5.5 3 0.034 46 11-31 0-7.5, 64
SEM 0.26 1.6/2.5 1 0.011 14 11-31 2-9, 60

* Fetal weight in kilograms at autopsy. Fraction of distal aortic flow at sensor level that flows through the umbilical vessels; the numbers signify the number of femoral arteries ligated at surgery and the placental flow fractions determined by microspheres and cord occlusion, respectively. The coefficient of linear correlation between the number of vessels tied and the mean placental flow fraction is 0.70, P < 0.05. NR, not recorded. From fetal femoral vein blood. Assumed placental flow fraction of 78%. With respect to intrauterine pressure: PFu, umbilical vein pressure; Pa, uterine vein pressure. Not experimentally varied. After 20 mg/kg fetus hexamethonium iv.

Effect of graded increases in umbilical vein pressure. Published evidence for a surrounding pressure of about 15 mmHg consists of the demonstration that an increase in umbilical venous pressure neither affects umbilical artery pressure nor flow if the increase is less than 15 mmHg (2, 11). The inserted diagram in Fig. 3 explains the presumed mechanism. In our preparations, the pressure and flow in the umbilical artery could not be enforced to remain constant during venous occlusion, but it was found that whereas umbilical blood flow changed, arterial pressure had only a slight tendency to rise (see, for instance, Fig. 6).

Graded occlusions of the umbilical vein were made of 0.3-2 min duration, and during each occlusion, pressures and flows were measured when umbilical venous pressure was steady. Table 1 shows how many data sets were recorded in each animal. These data sets were separated into classes of similar umbilical artery pressures, and each class was plotted as in Fig. 3.

The top diagram in Fig. 3 shows that in this animal, when umbilical artery pressure was between 27.0 and 29.4 mmHg, umbilical blood flow dropped, even after minute increases in umbilical vein pressure; points measured during the same occlusion are connected by lines. The dotted line in the top diagram indicates the relation one might expect if there had been a surrounding pressure of 15 mmHg. The bottom diagram of Fig. 3 shows the results from the three classes of arterial blood pressures that were necessary to accommodate all experimental data obtained on animal 2. In none of these do we see evidence of a surrounding pressure, and each of the three groups is compatible with an extrapolation (dotted lines) to zero flow when venous pressure rises to arterial levels.

A surrounding pressure can be detected only with changes in venous pressure below the surrounding pressure. For this reason, numerous mild occlusions were...
FIG. 2. Complete cord occlusion for determination of nonplacental flow fraction in distal aorta. Duration of occlusion was 11 s (see time marks). Completeness of occlusion is testified by equalization of umbilical arterial (PFA) and venous (PFV) pressures distal of occluder and by fact that venous pressure does not continue to rise; apparent rise during second half of occlusion is a properly transmitted spontaneous fluctuation in intrauterine pressure (PFe). Within 5 s aortic flow (QFe) has dropped to about 80 ml/min, and delay is accounted for by time constants of flowmeter and polygraph damping. In this recording, zero pressure on all pressure tracings is atmospheric pressure at a level of 1.9 cm above miduterine level. One and one-half millimeters Hg must be added to obtain intramaterine pressure from recording on Channel I. Fetal venous pressure is about 12 mmHg above intrauterine pressure before occlusion and 18 mmHg during occlusion. Maternal venous pressure (PMV) is about 1 mmHg. Note background of spontaneous fluctuations in pressure and flows before occlusion against which experimentally induced changes must be observed (animal 1).

made, and only relatively few occlusions were made that raised umbilical vein pressure above 15 mmHg.

Umbilical vein pressures were experimentally changed in 10 of the 11 animals over ranges of pressures indicated in Table 1. In none of these animals did we find evidence of a surrounding pressure. The smallest increase in umbilical vein pressure that could be reliably made against the background of spontaneous fluctuations in conscious animals was about 2.5 mmHg, and a surrounding pressure, if it exists, must be less than that in normal animals.

Fetal heart rate recordings were made in four animals. It was found, however, that fetal heart rate did not vary systematically with umbilical vein pressure during the temporary occlusions employed in this study. No further heart rate recordings were, therefore, made in the remaining animals.

Effect of graded increases in uterine vein pressure. The previous reports on perfused preparations show that maternal uterine vein pressure affects fetal placental surrounding pressure. It appeared possible that the absence of a detectable surrounding pressure in our animals was due to a lower uterine vein pressure in normal animals than in anesthetized ewes in a supine position.

Maternal uterine vein pressure was elevated in four ewes over the ranges of pressures indicated in Table 1. Maternal arterial blood pressure did not change during the occlusions. The effect of an increase in uterine vein pressure on fetal umbilical blood flow is shown in Fig. 4. The dotted line in Fig. 4 shows the expected relationship if uterine vein pressure elevates a surrounding pressure by an equal amount, as found previously in perfused preparations (2). It is clear that the experimental results in Fig. 4 are not compatible with an effect of

FIG. 3. Relation between umbilical blood flow and umbilical vein pressure when data are divided into classes of similar umbilical artery pressure (PFA). Top diagram for PFA = 27.0-29.4 mmHg. Points from data obtained during same occlusion are connected by lines in both diagrams. Dotted line in top diagram is expected relationship if a surrounding pressure of 15 mmHg must be exceeded before venous pressure can affect flow (see insert). When fetal venous pressure rises to arterial level (indicated by arrows underneath pressure scale), expected flow is zero; these extrapolations are indicated by dotted lines in bottom diagram (data from animal 2).
uterine vein pressure on the fetal umbilical circulation. Essentially identical results were obtained in all four animals.

In order to confirm this apparent absence of a surrounding pressure even when uterine vein pressure is elevated, fetal cord occlusions were repeated in the presence of increased uterine vein pressures in three animals. Figure 5 shows the results from animal 9. It appears to us that all data, regardless of the level of uterine vein pressure, belong to a single population; these results, therefore, are similar to those obtained without elevation of uterine vein pressure in Fig. 3 and are incompatible with the existence of a surrounding pressure.

Effect of anesthesia and supine position of the ewe. In order to determine whether anesthesia and a supine position could explain the difference between the results in previous and present experiments, two ewes (8 and 9) were given a light halothane anesthetic after the completion of the experiments described above and turned on their backs. No changes in fetal flow, umbilical artery pressure, or vein pressure were observed with this level of anesthesia.

Figure 4 (animal 8) shows that elevation of uterine vein pressure still affected neither umbilical flow nor umbilical arterial blood pressure. Figure 6 (animal 9) shows that even minute increases in umbilical vein pressure still caused immediate and stable decreases in umbilical blood flow. The difference between fetal umbilical arterial and venous pressures was approximately proportional to the difference between total distal aortic flow and the previously determined nonplacental part thereof. Figure 6 (bottom) summarizes the data from this animal for fetal arterial blood pressures between 33.5 and 39.5 mmHg above intrauterine pressure. There is no evidence of a surrounding pressure, even at the highest maternal uterine vein pressures. Compared to Figs. 5 (same animal) and 3, the data appear to be more consistent. This is due to the reduction in spontaneous fluctuations in fetal pressures and flows by the anesthetic.

Effect of ganglic block. To rule out the unlikely possibility that the decreases in umbilical blood flow were caused by a hitherto unknown autonomic reflex, the last animal (11) of this series was prepared with an umbilical cord occluder, a flow sensor, and catheters. On the 3rd day after surgery, it was first established that small elevations in umbilical vein pressure caused corresponding decreases in flow, as in all other studied animals. The fetus was then given hexamethonium (20 mg/kg body wt) intravenously as a single dose which was repeated at 30-min intervals. This dose is 2-3 times larger than the minimum necessary for complete ganglionic blockade in a sheep fetus (4, 7). A decrease in umbilical resistance to flow of less than 10% was found, probably due to a decrease in hematocrit which is commonly observed after injection of this drug in intact sheep fetuses (7). In all other respects, the results of elevations in umbilical vein pressure were identical to those recorded before the administration of the drug. Again, there was no evidence of a surrounding pressure. This experiment was performed on the 1st day after surgery also (data not included in Table 1), since it was the last available sheep of the season. The results of that experiment were the same as the results described above.

DISCUSSION

We considered whether the decreases in distal aortic blood flow induced by graded occlusion of the umbilical veins could have been decreases in nonplacental (somatic) flows rather than in placental flows. The reflex mechanism to be considered would consist of the sequence: inflation of occluder, diminished venous return,
Fetal placental fallopian with an immediate fall in distal aortic flow with no subsequent intensification. 2) If baroceptor activation occurred, an increase in fetal heart rate should have been observed, yet no systematic change in fetal heart rate was recorded. 3) No fall in arterial blood pressure was found that could have triggered somatic vasoconstriction; in fact, a (small) rise in arterial pressure, distal to the occluder, usually accompanied venous occlusion (Fig. 6). 4) Changes in somatic flow would have had to be relatively much larger than the changes in placental flow to cause similar decreases in distal aortic flow. For instance, a 10% decrease in distal aortic flow, such as was regularly recorded with small occlusions, would have required a 50% decrease in somatic flow if umbilical blood flow remained unchanged. 5) The observation that ganglionic blockade did not affect the experimental results of venous occlusion is consistent with the conclusion that the recorded decreases in flow were due to decreases in umbilical blood flow and inconsistent with the conclusion that they were due to reflex decreases in somatic flow.

It is our uniform experience that changes in flow occur immediately upon partial occlusion of the veins in the umbilical cord and reverse immediately upon release (Figs. 2 and 6). Reflex alterations in somatic flow of chemoreceptor origin are further incompatible with the persistence of the responses after ganglionic blockade. Local chemoreceptor responses would have caused increases rather than decreases in distal aortic flow. We conclude, therefore, that the observed changes in distal aortic flow are almost entirely changes in umbilical blood flow.

Umbilical blood flow constitutes more than 30% of fetal cardiac output (6). In the absence of powerful vaso-motor control in the near-term sheep fetus (7), partial occlusion of the umbilical circuit should cause an increase in peripheral resistance and in arterial blood pressure if venous return and cardiac output were unaffected. In the absence of an increase in umbilical resistance to flow, were that possible, partial cord occlusion would cause a decrease in venous return and a decrease in arterial blood pressure. In the near-term sheep fetus, these two opposite mechanisms appear to be almost equipotent; usually, only a very slight increase in arterial blood pressure followed a graded occlusion of the cord. One would suspect, then, that the umbilical veins are not very compliant, and that the volumes of blood sequestered behind the occluder were relatively small. Figure 2 reinforces that view. It shows that upon sudden complete occlusion of the cord, the pressure in the umbilical vein rises about half as much as the decrease in the pressure in the umbilical artery. Since the equalization of the pressures is due to the transfer of a certain volume of blood from the arterial into the venous system after occlusion, one concludes that the compliance of the umbilical veins is only 2 or 3 times that of the umbilical arteries, a significant deviation from the usual venoarterial ratio of about 20.

This observation is consistent with the results of a recent study in which independent increases in either umbilical artery or vein pressures resulted in similar changes in fetal placental vascular volumes (1).

If a capillary surrounding pressure did exist in the reduction in fetal cardiac output, reduction in fetal arterial blood pressure, baroceptor-mediated increases in somatic peripheral resistance, and heart rate.

The experimental results argue against this possibility. 1) Fetal reflex vasoconstriction requires several seconds to manifest itself and at least 1 min for its full development (3), whereas our recordings (Fig. 6) showed an immediate fall in distal aortic flow with no subsequent intensification. 2) If baroceptor activation occurred, an increase in fetal heart rate should have been observed, yet no systematic change in fetal heart rate was recorded. 3) No fall in arterial blood pressure was found that could have triggered somatic vasoconstriction; in fact, a (small) rise in arterial pressure, distal to the occluder, usually accompanied venous occlusion (Fig. 6). 4) Changes in somatic flow would have had to be relatively much larger than the changes in placental flow to cause similar decreases in distal aortic flow. For instance, a 10% decrease in distal aortic flow, such as was regularly recorded with small occlusions, would have required a 50% decrease in somatic flow if umbilical blood flow remained unchanged. 5) The observation that ganglionic blockade did not affect the experimental results of venous occlusion is consistent with the conclusion that the recorded decreases in flow were due to decreases in umbilical blood flow and inconsistent with the conclusion that they were due to reflex decreases in somatic flow.

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If a capillary surrounding pressure did exist in the
placenta of the near-term sheep fetus, small increases in umbilical vein pressure should not have affected fetal placental blood flow and arterial pressure. Having reviewed various known perfusion artifacts and a variety of hypothetical consequences of anesthesia and position of the ewe, the authors remain unable to explain how surrounding pressures could have been found in perfused preparations of sheep placentas in other laboratories (2, 10, 11). Although mechanical pressure of the wall of the (opened) uterus on the cannulas or cord of the perfused umbilical preparations could perhaps have created a Starling resistor effect, such an artifact could still not explain the influence of maternal uterine vein pressure on the apparent surrounding pressure (2, 11). The present experiments, however, that in the unanesthetized standing sheep, no surrounding pressure could be found, and this conclusion remained valid after anesthesia of the ewe, with the ewe in a supine position and after elevation of the pressure in the uterine veins.

Surrounding pressure promised to be a major regulator of fetal placental blood flow. This appears not to be the case. Fetal placental blood flow is determined by the difference between fetal arterial and venous blood pressures, and the fetal placental resistance to flow. The great rise in umbilical blood flow during fetal growth must be explained in terms of these variables alone.

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