Regional conductance changes during hemorrhage in pregnant and nonpregnant conscious rabbits

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Brooks, Virginia L., Colleen M. Kane, and Lisa S. Welch. Regional conductance changes during hemorrhage in pregnant and nonpregnant conscious rabbits. Am. J. Physiol. 277 (Regulatory Integrative Comp. Physiol. 46): R675–R681, 1999.—Late pregnant (P) conscious rabbits are less able to maintain arterial pressure during hemorrhage than nonpregnant (NP) animals. This study tested the hypothesis that the difference is due in part to less reflex vasoconstriction when the rabbits are P. Rabbits (n = 14) were instrumented with arterial and venous catheters as well as ultrasonic flow probes around the superior mesenteric, renal, and/or terminal aortic arteries. Pregnancy increased (P < 0.05) blood volume [235 ± 5 (P) vs. 171 ± 3 (NP) ml], terminal aortic conductance [1.88 ± 0.11 (P) vs. 0.98 ± 0.06 (NP) ml·min⁻¹·mmHg⁻¹], mesenteric conductance [1.20 ± 0.19 (P) vs. 0.80 ± 0.05 (NP) ml·min⁻¹·mmHg⁻¹], and heart rate [191 ± 4 (P) vs. 162 ± 3 (NP) beats/min] and decreased arterial pressure [59 ± 1 (P) vs. 67 ± 2 (NP) mmHg; P < 0.05]. Renal conductance was unaltered. The rabbits were bled in both the NP and P states at 2% of the initial blood volume per minute until arterial pressure fell below 45 mmHg. Arterial pressure fell with less blood loss in P rabbits [28 ± 2% (P) vs. 39 ± 2% (NP) of initial blood volume; P < 0.001]. Terminal aortic conductance decreased (P < 0.001) before the pressure fall in both groups, but the response was reduced in P rabbits. Mesenteric and renal conductances did not change in either group before the blood pressure fall. During the pressure fall, terminal aortic conductance increased (P < 0.05) only in NP rabbits. Mesenteric conductance increased in both groups. In summary, rabbits in late gestation are less able to maintain arterial pressure during hemorrhage, at least in part because of reduced vasoconstriction in tissues perfused by the terminal aorta.

baroreceptor reflex; pregnancy; mesenteric blood flow; terminal aortic blood flow; renal blood flow

The hemodynamic response to hemorrhage in conscious animals typically consists of two phases: an initial nonhypotensive phase followed by an abrupt transition to hypotension (31). During the nonhypotensive phase, blood pressure maintenance is achieved largely by activation of the baroreceptor reflex and sympathoexcitation (31). Recent data suggest that this homeostatic response is attenuated during gestation in several species and is associated with decreased gain of baroreflex control of heart rate and sympathetic activity (5). However, whether a change in the baroreflex is the cause for the reduced ability to maintain arterial pressure during hemorrhage in pregnant animals has not been directly determined.

The initial hemorrhage-induced sympathoexcitation supports arterial pressure in part by causing vasoconstriction, in particular to muscle and skin (31). Therefore, if reduced reflex function is the cause of intolerance displayed by pregnant animals to maintain arterial pressure, then it would be expected that less vasoconstriction, and therefore smaller increases in vascular resistance, would be produced during the nonhypotensive phase. Moreover, because the hypotensive phase is mediated by withdrawal of sympathetic tone (31), then, if initial reflex sympathoexcitation is blunted during pregnancy, the vasodilation that occurs during the hypotensive phase might also be less. The present experiments were designed to test these hypotheses. Conscious rabbits instrumented with regional flow probes were studied in both the nonpregnant and pregnant state to determine if reflex vasoconstriction observed during the initial phase of hemorrhage is reduced and if the reflex vasodilation during the hypotensive phase is less during gestation.

METHODS

All studies were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and were approved by the institutional (Oregon Health Sciences University) Animal Care and Use Committee.

Surgical preparation. Female (n = 14) New Zealand White rabbits weighing 3.43 ± 0.03 kg (nonpregnant) were used for these experiments. The rabbits were obtained when they were 14–15 wk old and allowed a 1-wk acclimatization period. Surgery was then performed to implant nonocclusive abdominal aortic and vena cava catheters and flow probes as previously described (13). Briefly, the animals were initially anesthetized (1 ml/kg im) with a cocktail containing 5:2:5:1 of ketamine (100 mg/ml), xylazine (20 mg/ml), and acepromazine (10 mg/ml) and a surgical plane of anesthesia was maintained with 1:10 ketamine-0.9% NaCl solution administered intravenously as needed. A midline abdominal incision was made, and indwelling polyethylene catheters with Silastic tips were implanted in the abdominal aorta (one) and vena cava (two). The catheters were tunneled from the abdominal cavity, subcutaneously, and were exteriorized at the nape of the neck. The rabbits also received 1–2 ultrasonic flow probes (2 or 3SB, Transonic Systems, Ithaca, NY) around the terminal aorta, just proximal to the bifurcation, the superior mesenteric artery, and/or the left renal artery. Ten rabbits received one probe; four rabbits received two (2 with terminal aorta/renal; 1 with terminal aorta/mesenteric; 1 with mesenteric/renal). Probes were wrapped with sterile silicon sheeting to prevent fat invagination and to lengthen probe life span. Flow probe leads were also tunneled subcutaneously to the nape of the neck and protected in a 3.5-cm plastic pill box that was sutured to the rabbits’ skin. The rabbits were given...
Hemorrhage in pregnant rabbits

Penicillin G Procaine (60,000 U im) just before and the day after the surgery. The animals were given Buprenex (0.3 ml of 0.3 mg/ml im) 2–3 h after surgery and received an analgesic (50 mg acetaminophen) by mouth three times per day for 3–4 days after surgery. The neck incision was treated with topical nitrofurazone antibacterial dressing for 1 wk after surgery. Catheters were flushed immediately after surgery and then three times weekly using sterile 0.9% NaCl and filled with heparin (1,000 U/ml) to maintain patency.

Animals were allowed at least 2 wk for recovery from surgery. During this time the rabbits were transitioned from a high-fiber diet (Ralston Purina, 5326) to a high-protein diet (Ralston Purina, 5321), increasing 10% high protein/day for 10 days. The rabbits were then maintained on 150 g/day of the high-protein diet (0.25% sodium and 16.2% protein) to enhance breeding efficiency. All animals were allowed free access to distilled water. During recovery, the rabbits were also trained to rest quietly in a specially designed opaque Plexiglas box that was used to restrain the rabbits during experiments. Room temperature was kept between 64 and 68°F, and a 16-h light cycle was maintained for optimum breeding.

Hemorrhage protocol. The rabbits were first hemorrhaged in the nonpregnant state. Afterwards, the animals were bred with noninstrumented proven male breeder rabbits, and this was considered day one of pregnancy. The hemorrhage was repeated in each animal after 28–30 days of pregnancy (term is 31 days). Pregnancy was verified by palpation at midgestation by a veterinarian. All rabbits delivered successfully (number of kits: 7 ± 1; range: 2–12).

Blood volume increases significantly during pregnancy. Therefore, to produce equivalent hemorrhages in the rabbits when they were pregnant and nonpregnant, the animals were bled as a function of their initial blood volume. A blood volume of 49 ml/kg was assumed and calculated for each rabbit in the nonpregnant animals (6), blood volume was estimated in the pregnant animals the day before the experiment by measuring the volume of distribution of technetium-labeled red blood cells (2).

On the day of the experiment, the rabbits were placed in the Plexiglas box and allowed 30–45 min to equilibrate. Arterial pressure and heart rate were measured continuously via the aortic catheter using a Statham pressure transducer, a Grass Tachometer, and a Grass Polygraph. Flow probes were connected to a model T206 Transonic flowmeter, and output was displayed on the polygraph. A venous catheter was attached to sterile tubing, which was threaded through a peristaltic pump and connected to a sterile plastic bag.

After injecting 1 ml iv heparin (1,000 U/ml), baseline hemodynamic measurements were made for ~15 min. Then the hemorrhage was begun by withdrawing venous blood into the sterile bag at a rate of 2% of the initial total blood volume per minute. The hemorrhage was continued until arterial pressure abruptly fell below 45 mmHg and was then stopped. A 15-min period was allowed for stabilization, and then the shed blood was returned to the rabbit by reversing the direction of the pump.

Data and statistical analysis. For Figs. 2 and 3 and Table 1, ~30-s averages of arterial pressure, heart rate, and flows were obtained from the polygraph recordings every 2.5 min beginning with the start of the hemorrhage. However, this method of analysis tends to obscure the details of the rapid pressure fall, because pressure drops at a different time in each rabbit. Therefore, in Figs. 3–7, hemodynamic measurements were also quantified from the continuous pressure tracing, beginning with the lowest pressure point or pressure nadir, to determine the between-group differences in the hypotensive phase. Differences in basal values between pregnant and nonpregnant rabbits were determined with the paired t-test (33). Between-group differences in the hemodynamic responses to hemorrhage were determined using two-way ANOVA for repeated measures (randomized block) and the post hoc Tukey-Kramer procedure (25, 33). Because, for some variables, basal values were different between groups, this analysis was used to determine at which times significant differences from control could be detected within a group. All statistics were performed using GB-STAT (Dynamic Microsystems, Silver Spring, MD).

RESULTS

Effects of pregnancy on basal hemodynamic values. As indicated in Fig. 1, several characteristics of the cardiovascular system were altered during pregnancy in conscious rabbits. Arterial pressure decreased, and heart rate increased. Blood volume was also increased (171 ± 3 ml, nonpregnant; 225 ± 5 ml, pregnant, P < 0.05). In the five pregnant rabbits in which body weight was measured, the normalized blood volume (51.1 ± 1.7 ml/kg) was similar to that previously published (6). Terminal aortic flow increased from 65.1 ± 3.2 to 109.6 ± 4.7 ml/min (P = 0.0001); however, neither renal (25.7 ± 2.0, nonpregnant; 24.9 ± 2.1 ml/min, pregnant) nor mesenteric (54.1 ± 4.2, nonpregnant; 72.7 ± 11.5 ml/min, pregnant) flows were significantly changed. Nevertheless, because these flows were produced at

Table 1. Change in conductance (%control) during nonhypotensive hemorrhage in pregnant and nonpregnant rabbits

<table>
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<th>Time, min</th>
<th>-2.5</th>
<th>0</th>
<th>2.5</th>
<th>5</th>
<th>7.5</th>
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<tr>
<td>NP</td>
<td>100 ± 1.6</td>
<td>101.2 ± 1.9</td>
<td>93.2 ± 1.6</td>
<td>88.2 ± 2.8*</td>
<td>79.9 ± 3.7*</td>
<td>81.1 ± 2.8*</td>
<td>79 ± 4.5*</td>
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<tr>
<td>P</td>
<td>96.8 ± 1.1</td>
<td>101.1 ± 1.2</td>
<td>98.9 ± 1.3</td>
<td>93 ± 1.6</td>
<td>91.9 ± 1.7</td>
<td>88.2 ± 2.3*</td>
<td>87.5 ± 3.3*</td>
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<td>Renal conductance</td>
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<tr>
<td>NP</td>
<td>100.5 ± 0.2</td>
<td>99.1 ± 2.1</td>
<td>101 ± 3.6</td>
<td>99.8 ± 4.3</td>
<td>96.1 ± 5.7</td>
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</tr>
<tr>
<td>P</td>
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<td>99 ± 3.3</td>
<td>95.4 ± 4.8</td>
<td>94.1 ± 5.0</td>
<td>87.5 ± 6.3</td>
<td>80.6 ± 6.1*</td>
<td>85.2 ± 7.5</td>
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<tr>
<td>NP</td>
<td>99.1 ± 1.2</td>
<td>98.6 ± 1.5</td>
<td>100.2 ± 1.9</td>
<td>97.3 ± 3.1</td>
<td>95.8 ± 5.3</td>
<td>94.1 ± 5.3</td>
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<tr>
<td>P</td>
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<td>94.8 ± 4.1</td>
<td>90.7 ± 4.3</td>
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Values are means ± SE. NP, nonpregnant; P, pregnant. *P < 0.05 compared with time zero.
reduced arterial perfusion pressure, terminal aortic and mesenteric conductances were increased (Fig. 1). On the other hand, although five of six rabbits exhibited an increase in renal conductance, this response was not significant (Fig. 1).

Responses of pregnant and nonpregnant rabbits to hemorrhage: the nonhypotensive phase. Because pregnancy causes changes in each phase of hemorrhage, the results of the two phases will be considered separately.

To determine differences in the nonhypotensive phase, the data were aligned to the beginning of hemorrhage. Figure 2 illustrates that arterial pressure decreased in both groups during hemorrhage; however, a smaller degree of blood loss was required to produce the pressure fall when the rabbits were pregnant. Pressure decreased below 45 mmHg after 39.2 ± 1.5% of the initial blood volume was removed in nonpregnant rabbits, whereas only 27.6 ± 1.8% blood volume loss was required when the rabbits were pregnant (P < 0.001). Heart rate increased in both groups (Fig. 2). Due to the vasoconstriction occurring in the terminal aortic vascular bed, terminal aortic conductance decreased in both groups (Table 1). However, a significant decrease in conductance was apparent with less blood loss before pregnancy (Table 1). On the other hand, mesenteric conductance did not change in either group during the nonhypotensive phase (Table 1). Renal conductance also did not change initially in virgin rabbits, but decreased briefly when the rabbits were pregnant (Table 1).

These data suggest that reflex vasoconstriction in the terminal aortic vascular bed is diminished during pregnancy. However, the data were normalized as percent change from control, so that comparisons could be made between groups with widely divergent starting values in terminal aortic conductance. Because it could be argued that the smaller response in pregnant animals was due to the normalization, the data were also analyzed as absolute change from control. Figure 3A illustrates that the absolute decrease in conductance was also delayed when the rabbits were pregnant.

Responses of pregnant and nonpregnant rabbits to hemorrhage: the hypotensive phase. To emphasize between-group differences in the pressure fall, the data were also aligned to the pressure nadir, which occurs at
After a period of arterial pressure maintenance, pressure rapidly decreased (Fig. 4). Interestingly, the magnitude of the pressure fall was reduced during pregnancy (difference in pressure between the times 5 min before nadir and the nadir: 37 ± 6, nonpregnant; 19 ± 3 mmHg, pregnant; \( P < 0.0001 \)). This decrease in pressure was associated with a temporary, sharp increase in terminal aortic and mesenteric conductances in nonpregnant rabbits \( (P < 0.01; \text{Figs. 5 and 6}) \). During gestation, mesenteric conductance also increased during the hypotensive phase \( (P < 0.01; \text{Fig. 6}); \) however, terminal aortic conductance did not change, depicted either as percent change \( (\text{Fig. 5}) \) or as absolute change \( (\text{Fig. 3B}) \). Renal conductance did not increase consistently during the pressure fall in either state \( (\text{Fig. 7}) \).

**DISCUSSION**

The hemodynamic response to hemorrhage in conscious animals consists of two phases: an initial nonhypotensive phase followed by a rapid fall in arterial pressure \( (31) \). The results of the present study reaffirm that there are changes in both phases during pregnancy in conscious rabbits \( (6) \). More specifically, during gestation, arterial blood pressure decreases with less blood loss and the magnitude of the pressure fall is smaller. The important new findings are that in the nonhypotensive phase 1) neither nonpregnant nor pregnant rabbits exhibit significant decreases in mesenteric conductance and 2) conductance of the vascular bed perfused by the terminal aorta decreases in both reproductive states, but the response is attenuated during pregnancy. During the hypotensive phase, 3) mesenteric conductance increases similarly in pregnant and nonpregnant rabbits, 4) renal conductance does not increase consistently in either group, whereas 5) terminal aortic conductance increases in nonpregnant but not in pregnant rabbits. These findings will now be discussed, focusing first on the nonhypotensive phase.

![Fig. 3](image-url) Absolute changes in terminal aortic conductance during hemorrhage in nonpregnant (■) and pregnant (□) conscious rabbits \( (n = 7) \). A: nonhypotensive phase. Time zero indicates beginning of hemorrhage. B: hypotensive phase. Time zero indicates nadir in arterial pressure. *\( P < 0.05 \) compared with time zero.

![Fig. 4](image-url) Arterial pressure changes during hemorrhage in nonpregnant (■) and pregnant (□) rabbits \( (n = 14) \). Data are aligned to arterial pressure nadir (time zero).

![Fig. 5](image-url) Changes in terminal aortic conductance in nonpregnant (■) and pregnant (□) rabbits \( (n = 7) \). Data are aligned to pressure nadir (time zero).
In conscious nonpregnant animals, blood pressure maintenance during hemorrhage is achieved via baroreflex-induced sympathoexcitation, which causes vasoconstriction primarily in the splanchnic circulation, muscle, and skin (31). On the other hand, neither renal nor mesenteric conductances change appreciably (31). Complementary results for the renal and mesenteric beds were found in nonpregnant and pregnant animals in the present study. However, although terminal aortic conductance decreased in both groups, the response was more slowly developing when the rabbits were pregnant, despite the tendency to enter the hypotensive phase more rapidly. These results suggest that the more rapid progression to hypotension during pregnancy is due in part to less vasoconstriction in tissues perfused by the terminal aorta.

Few previous studies have investigated pregnancy-induced changes in the degree of vasoconstriction produced by hemorrhage. In an elegant series of studies, Humphreys and Jöels (14–19) examined whether pregnancy influences reflex-induced changes in total or hindquarter vascular conductance using hemorrhage or decreased pressure in the isolated carotid sinus as a means to activate the baroreflex. Two important methodological differences precluded careful study of the initial nonhypotensive phase in the experiments of Humphreys and Jöels and therefore a direct comparison of these results with those of the present study. First, the rabbits were anesthetized, and anesthesia is known to markedly blunt baroreflex function (31, 35). Second, the rate of bleeding was rapid, and the rabbits quickly exhibited hypotension. Nevertheless, in the period immediately after the hemorrhage, hypotension was greater and the degree of vasoconstriction was reduced in the pregnant animals, and this difference was abolished by sinoaortic denervation (18). These results support the premise that reflex-induced vasoconstriction, particularly in the hindlimb, is blunted in rabbit pregnancy.

Several possible mechanisms can explain the blunted response of pregnant rabbits. One possibility, which is supported by significant previous work (5), is that baroreflex-mediated increases in sympathetic activity are reduced. Second, because the pressor effect of several vasoconstrictors can be attenuated during pregnancy (23), the response of the vasculature to a given level of sympathetic activity may be less. This idea has been extensively investigated in recent years, and it appears that pregnancy may alter vascular responsiveness. However, the specific pregnancy-induced alterations vary between vascular beds (32, 34). No evidence for reduced reactivity to norepinephrine has been found in pregnant rats or sheep, specifically in the hindquarter vascular bed (1, 27, 34). In rabbits, Humphreys and Jöels reported that although the hindquarter circulation was more dilated, perhaps due to increased compliance, vasoconstriction induced by stimulation of sympathetic nerves was similar in pregnant and nonpregnant animals (17). Thus it is unlikely that the responsiveness of vessels in hindquarter muscle and skin to sympathetic stimulation is reduced during pregnancy.

Prior research suggests that sympathetic innervation of the uterus decreases during pregnancy and that reflex vasoconstriction in this vascular bed is absent or diminished (22, 30). Moreover, the rabbit uterine artery originates from the internal or external iliac artery (8), which is distal to the placement of the terminal aortic flow probe in the present study. Therefore, because terminal aortic flow encompasses not only skeletal and cutaneous but also uteroplacental flows, a third explanation is that uteroplacental portion of terminal aortic flow is refractory to reflex increases in sympathetic activity and this reduced responsiveness underlies the blunted vasoconstriction in this vascular bed. Although we cannot completely dismiss this possibility, it cannot be the sole explanation for the following reasons. First, the absolute decrease in terminal aortic conductance was delayed when the rabbits were pregnant. Thus, even if the uteroplacental circulation were completely unresponsive to reflex increases in sympathetic activity, it appears that the fall in conductance in the
remaining vasculature was also reduced. Second, a survey of the literature reveals that uteroplacental blood flow in the rabbit near term amounts to 30–35 ml/min, which is about 6% of the cardiac output (4, 9, 11, 12, 20, 24). Although this increase in flow can almost completely explain the pregnancy-induced increase in terminal aortic flow that we observed, a complete lack of vasoconstriction in such a small vascular bed cannot solely cause the more rapidly induced hypotension observed in the pregnant rabbits.

Korner and colleagues (21) emphasized that in addition to reflex vasoconstriction, hemorrhage simultaneously causes a vasodilatory response mediated by local vascular mechanisms. Thus a fourth explanation for the blunted terminal aortic vasoconstriction is that local vasodilatory actions are increased in the pregnant rabbits. In view of evidence that nitric oxide production may be increased during gestation, particularly in the uteroplacental vascular bed (26, 32), this possibility deserves further investigation.

The present results demonstrate that gestation also modifies the hypotensive phase of hemorrhage. In particular, the fall in arterial pressure and the rise in terminal aortic conductance were markedly reduced when the rabbits were pregnant. Prior research has revealed that the fall in arterial pressure is mediated by withdrawal of sympathetic vasoconstrictor tone, whereas the recovery of pressure is mediated largely by hormonally induced (e.g., vasopressin and angiotensin II) vasoconstriction (31). Therefore, the smaller hypotensive response could be due to a smaller decrease in sympathetic activity or to greater hormonally mediated vasoconstriction. We have previously reported that hemorrhage-induced increases in vasopressin are normal, but increases in angiotensin II are enhanced in the pregnant rabbit (6). However, because the reactivity of the hindquarters to angiotensin II is greatly diminished during pregnancy in the rabbit and other species (1, 27, 28), an increased responsiveness to circulating vasoconstrictors is unlikely. Therefore, it appears that the sympathoinhibition that underlies the hypotensive phase is lost during pregnancy, at least in the terminal aortic vascular bed. The fact that the conductance increase in the mesenteric bed was not modified when the rabbits were pregnant suggests that there is not a change in the reflex per se. On the other hand, it could again be argued that the failure to vasoconstrict is due to the presence of the relatively unresponsive uteroplacental circulation. However, the complete lack of response is contrary to this argument. Instead, this result also supports the contention that reflex increases in sympathetic activity are blunted, at least in this vascular bed, during rabbit gestation, and the reduced sympathoexcitation leads secondarily to a reduced ability to withdraw sympathetic tone.

In summary, the present results demonstrate that rabbits in late gestation are less able to maintain arterial pressure during hemorrhage, at least in part because of reduced vasoconstriction in tissues perfused by the terminal aorta.

Perspectives

The inability to maintain arterial pressure during hemorrhage is a feature of pregnancy that has been noted by many investigators in several species (5). Although it has not been determined whether pregnant women also experience this difficulty, it is known that women in late pregnancy respond to orthostatic stress with smaller increases in systemic vascular resistance or in plasma norepinephrine levels (3, 7, 10, 29). Hemorrhage is a common result of normal delivery; therefore, an understanding of the mechanism of the change is clearly essential for effective patient care. Because these changes in cardiovascular homeostasis are associated with reduced baroreflex gain, we have speculated that the change in the baroreflex mediates the altered response to hemorrhage (5, 6). The present results are consistent with this speculation, because smaller decreases in conductance in the terminal aortic vascular bed were observed in the pregnant animals during the nonhypotensive phase. Nevertheless, because the responses of the renal and mesenteric beds were generally unaltered by pregnancy, it seems likely that other factors are involved. Two that merit further study are that local vascular vasodilatory mechanisms are enhanced or that reflex venoconstriction is reduced, and therefore the fall in cardiac output is greater, during rabbit gestation.

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