Repeated pregnancies (multiparity) increases venous tone and reduces compliance

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Dhawan, Vivek, Zoe L. S. Brookes, and Susan Kaufman. Repeated pregnancies (multiparity) increases venous tone and reduces compliance. Am J Physiol Regul Integr Comp Physiol 289: R23–R28, 2005. First published March 24, 2005; doi:10.1152/ajpregu.00034.2005.—In humans, multiparity (repeated pregnancy) is associated with increased risk of cardiovascular disease. In rats, multiparity increases the pressor response to phenylephrine and to acute stress, due in part to changes in tone of the splanchnic arterial vasculature. Given that the venous system also changes during pregnancy, we studied the effects of multiparity on venous tone and compliance. Cardiovascular responses to volume loading (2 ml/100 g body wt) and mean circulatory filling pressure (MCFP, an index of venomotor tone) were measured in conscious, repeatedly bred (RB), and age-matched virgin rats. In addition, passive compliance and venous reactivity of isolated mesenteric veins were measured by pressure myography. There was a greater increase in mean arterial pressure after volume loading in RB rats (+7.2 ± 2.5 mmHg, n = 8) than virgin rats (−1.4 ± 1.7 mmHg, n = 7) (P < 0.05). The increase in MCFP in response to norepinephrine (NE) was also greater in RB rats [half maximal effective dose (ED50) 3.1 ± 0.5 nmol·kg⁻¹·min⁻¹, n = 6] than virgins (ED50: 12.1 ± 2.7 nmol·kg⁻¹·min⁻¹, n = 6) (P < 0.05). Pressure-induced changes in passive diameter were lower in isolated mesenteric veins from RB rats (29.3 ± 1.8 μm/mmHg, n = 6) than from virgins (36.9 ± 1.3 μm/mmHg, n = 6) (P < 0.05). Venous reactivity to NE in isolated veins was also greater in RB rats (EC50: 2.68 ± 0.37×10⁻⁸ M, n = 5) than virgins (EC50: 4.67 ± 0.93×10⁻⁸ M, n = 8). We conclude that repeated pregnancy induces a long-term reduction in splanchnic venous compliance and augments splanchnic venous reactivity and sympathetic tonic control of total body venous tone. This compromises the ability of the capacitance (venous) system to accommodate volume overloads and to buffer changes in cardiac preload.

PREGNANCY IS ASSOCIATED with profound alterations in the cardiovascular and hormonal systems. It is unclear whether these changes ever revert to normal after pregnancy. It is also unknown how these pregnancy-related changes might affect risk factors for cardiovascular disease later in life. Epidemiological studies suggest that multiparity (repeated pregnancy), significantly increases the risk of cardiovascular disease long after reproductive activity has ceased (2, 23, 29, 30).

Evidence suggests that plasma levels of some reproductive hormones with cardiovascular activity, such as estrogen and prolactin, are permanently altered after pregnancy (4, 47). Animal studies have also revealed that repeated pregnancy causes degradation of vascular elastic tissue and increased incidence of atherosclerosis (45, 46). Moreover, it has been reported that renal vessels from multiparous rats have higher tone than those from virgins rats and that this is due to decreased endothelial nitric oxide (NO) (36). This is consistent with our finding that repeated pregnancy potentiates endothelium-dependent constriction in isolated mesenteric arteries exposed to phenylephrine and that both stress and intravenous infusion of phenylephrine induce a greater pressor response in conscious repeatedly bred (RB) rats than in age-matched virgin control rats (11).

The venous part of the circulation plays a critical role in cardiovascular regulation (13, 43). Given that there are significant alterations in the venous vasculature during pregnancy (18–21), we tested the hypothesis that these would persist to cause long-term functional and structural changes in the parous animal. Our aim in this study was to compare venous tone and venous compliance of RB and virgin rats; to this end, we measured mean circulatory filling pressure (MCFP) and mesenteric venous vasoactivity and compliance (pressure myography). We also compared the effects of volume loading on blood pressure responses of RB and virgin rats.

It is difficult in epidemiological studies to control for potentially confounding factors such as socioeconomic status and the psychological stresses of child rearing (31). Thus well-controlled animal studies are critically important. The rat is an excellent model for our study, as pregnancy-associated changes observed in rats are very similar to those found in humans (41), and, moreover, we can induce repeated pregnancies within a short interval of time.

MATERIALS AND METHODS

The experimental procedures were approved by the local Animal Welfare Committee in accordance with the guidelines issued by the Canada Council on Animal Care, which conforms to National Institutes of Health guidelines.

Animals and housing. Seven to eight-month-old female Long Evans retired breeder (RB) rats were obtained from Charles River (St. Foy, Quebec, Canada). These animals had undergone five pregnancies; their age at first pregnancy was 56 days. The control animals were aged-matched virgin rats (Charles River), raised in the same living conditions as the retired breeders. A period of at least 1 mo from arrival was allowed to elapse before the experiments were started, during which time, the rats were held in the University of Alberta animal facility on a 12:12-h light-dark cycle, in a humidity- and temperature-controlled environment. To prevent obesity, they were restricted to just three pellets (20 g) of food per day (27).

Blood Volume Measurement and Pressor Response to Volume Loading

Surgery. Rats were anesthetized with pentobarbital sodium (62 mg/kg body wt, ip), followed by atropine (0.1 ml, 0.4 mg/ml sc). Buprenorphine (0.01 mg/kg sc) was given after the completion of surgery. A nonocclusive cannula [inside diameter (ID): 0.51-mm; outside diameter (OD): 0.94-mm; Silastic, Dow Corning, Midland, Michigan] was implanted into the inferior vena cava (IVC) for infusing the volume load and for taking blood samples. Another

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Silastic cannula of the same external diameter was implanted in the jugular vein to infuse dye for blood volume measurement. A telemetric pressure transmitter (PAC-40, Data Sciences International, Arden Hills, MN) was implanted in the abdominal aorta to measure systemic blood pressure. Animals were allowed to recover for 1 wk after surgery and to regain their preoperative body weight.

**Blood volume measurements.** Plasma volume was determined by the Evans blue dye dilution method (26). Briefly, initial blood samples (0.25 ml) were taken. A solution (0.3 ml, 0.5%) of Evans blue (Baker Chemical, Phillipsburg, NJ) was injected and then flushed with 0.2 ml saline. Blood samples (0.15 ml) were taken from the IVC cannula at 10, 20, 30, 40, and 60 min, and the volumes replaced with isotonic saline infused through the same cannula. The blood samples were transferred to heparinized Microvette (Sarstedt, Aktiengesellschaft, Numbrecht, Germany) and centrifuged. Hematocrit was measured, and plasma was separated from red blood cells. The plasma samples (50 µl) were diluted in 950 µl of saline, and absorbance was measured at 605 nm on a spectrophotometer (LKB Biochrom, model 4049, Cambridge, UK). The readings were compared with standards obtained by adding 0, 1, and 2 µl of the 0.5% Evans blue solution to 50 µl initial plasma sample plus 950 µl saline. The plasma volume and blood volume were determined by extrapolation back to time zero.

**Blood pressure response to volume loading.** After 1 day acclimatization to the metabolism cages, baseline mean arterial pressure (MAP) was recorded for 1 h in conscious, unrestrained animals (PhysioTel Telemetric System, Data Sciences International). Rats were then challenged with a volume overload by infusing Pentaspan (2 ml/100 g·1·min⁻¹), (DuPont Pharma, Canadian Blood Bank services). These experiments were always conducted at the same time of day (10:00–12:00AM). Data were later analyzed off-line (Windaq, DATAQ Instruments, Akron, OH).

**MCFP**

**Surgery.** A separate group of rats was anesthetized using halothane anesthesia. Three polyethylene cannulas (PE-50, ID: 0.58 mm, OD: 0.97 mm; VWR International, Mississauga, Ontario, Canada) were implanted during the surgery: 1) right iliac vein to infuse drugs, 2) IVC via left femoral vein to measure central venous pressure (CVP), and 3) left iliac artery to measure systemic blood pressure. In addition, a saline-filled balloon-tipped catheter was placed through the right jugular vein into the right atrium (8). The balloon, when correctly positioned, caused an instantaneous decrease in HR and MAP accompanying an increase in CVP during inflation. All cannulas were filled with heparinized normal saline (25 IU/ml) and tunneled subcutaneously to the midscapular region of the back. At least 5 h, but less than 8 h, was allowed to elapse before MCFP was measured. This allowed for recovery from surgery and anesthesia but minimized the risk of thrombogenesis from the intracardiac balloon.

**Experimental protocol.** Unrestrained animals were placed in a small cage and allowed to eat and drink freely. Central venous and arterial cannulas were connected to Gould Statham pressure transducers, and baseline MAP, CVP, and heart rate were recorded for 20 min. MCFP was calculated using the formula MCFP = VPP + K (FAP – VPP) (33), where VPP and FAP represent the venous plateau pressure and the final arterial pressure, respectively; K is a constant representing the ratio of venous and arterial compliance (equals 1/60) (33). Venous and arterial pressures were measured during circulatory arrest induced by inflating the intracardiac balloon for ~5–7 s, until CVP had plateaued. We used the nonspecific adrenergic agonist norepinephrine (NE) because it has been reported that the rat venous side of splanchnic vascular bed constricts predominantly to α1–2 adrenergic agonists (35). To minimize the effects of NE on the heart, β-adrenergic receptors were blocked with propranolol (1 mg/kg iv). After a 10-min stabilization period, baseline MAP, HR, CVP, and MCFP measurements were made. After a further 10-min recovery period, dose-response curves to NE (1, 3, 10, 30, and 100 × 10⁻⁹ mol·kg⁻¹·min⁻¹) were constructed. At each dose, it took ~3 min for the MAP to plateau, at which point MAP, HR, CVP, and MCFP measurements were made. A 10-min recovery period was allowed between each dose of NE. This protocol has previously been used to make repeated measurements of venous tone (33).

**Isolated Vessel Study**

**Preparation of isolated vessels.** The rats were decapitated, and segments of the small intestine and attached mesentery were isolated (~10 cm from the ileo-caecal junction). Second-order mesenteric veins, ~2 mm in length, were dissected in cold (0–4°C) HEPES (concentration in mmol/l: 142 NaCl, 4.7 KCl, 1.17 MgSO₄, 1.56 CaCl₂, 1.18 K₂PO₄, 10 HEPES, and 5.5 glucose, at pH 7.4) and used to study venous reactivity. Third-order veins were dissected in Ca²⁺-free Dulbecco’s medium [concentration in mmol/l: 15 HEPES, 15 glucose, 1 sodium pyruvate, 25 sodium bicarbonate, and 1 µM EGTA with 1 g/l albumin (IgG and endotoxin-free) at pH 7.4] and used to study venous compliance.

**Venous reactivity.** Isolated veins were mounted on the cannulas (180–200 µm) of a myograph small-vessel chamber (CH2/2H, Living Systems Instrumentation, Burlington, VT), and the experiments were performed using blind-sac (no-flow) technique. Leaks were tested by increasing the intraluminal pressure to 5 mmHg using a pressure servo system (PS2000Q, Living Systems Instrumentation), and the system was considered to be leak-free if no drop in pressure occurred. During the equilibration period, the vessels were first exposed to an intraluminal physiological flow rate of 2 µl/min for 10 min to flush out metabolites and then stabilized at no-flow condition at 5 mmHg for 30 min. Temperature of the vessel chamber was maintained at 37 ± 0.5°C throughout the duration of the experiment using a temperature servo controller (Living Systems Instrumentation). Before the concentration response curve was constructed for NE, the vessels were incubated with propranolol (10⁻⁶ M) for 15 min to block the effect of NE on venous β-adrenergic receptors. The vessels were then exposed to a cumulative concentration-response regime of NE (1 × 10⁻⁹ to 1 × 10⁻⁶ M), and the changes in diameter were measured using a CCD camera (Sony) and a video dimension analyzer (Living Systems Instrumentation). EC₅₀, the concentration required to produce 50% of the maximum response, was calculated from sigmoidal plots (SigmaPlot, Systat Software) of concentration-response curves (%change of initial diameter) constructed for each individual vessel.

**Venous compliance.** The diameter-pressure relation of small mesenteric vessels was examined, by pressure myography (Living Systems Instrumentation), using Ca²⁺-free medium as previously described (6). Venous compliance was calculated as the ratio of Δ internal diameter: Δ pressure, in the physiological range of 4–8 mmHg intraluminal pressure.

**Statistical analysis.** Time-, dose-, and pressure-dependent responses were analyzed using repeated-measures two-way ANOVA, followed by post hoc analysis with the Student-Newman-Keuls test. For comparisons between two sets of data such as ED₅₀, Student’s t-tests for unpaired data were used. In the venous reactivity study, where we predicted that EC₅₀ of veins from RB would be less than that from virgin rats, we used a one-tailed t-test for unpaired data. All data are presented as means ± SE of mean. All results were considered statistically significant at P < 0.05.

**RESULTS**

**Baseline parameters.** The RB rats were slightly heavier than the age-matched virgin rats [RB: 381 ± 6 g, n = 25 vs. virgin rats (V): 334 ± 6 g, n = 29; P < 0.05]. Two different protocols were used to measure cardiovascular parameters in the volume loading and MCFP studies; animals in the former group were allowed to recover for at least 1 wk after surgery, while MCFP
was measured only 5 h after anesthesia and surgery. We have therefore reported the baseline parameters separately in Table 1. There were no significant differences between resting MAP or HR of the RB and virgin rats. However, blood volume was lower in the RB rats (RB: 5.9 ± 0.1 ml/100 g, n = 4; V: 6.9 ± 0.3 ml/100 g, n = 5, *P* = 0.025).

Response to volume loading. There was a greater increase in MAP to volume loading in RB animals than aged-matched virgin control rats (Fig. 1A). The changes in HR in the animals from both the groups were similar, although there was a significant increase from baseline in the RB rats (Fig. 1B).

Response to NE (MCFP and MAP). There was no difference in baseline MCFP between the two groups, although it tended to be lower in RB rats (5.7 ± 0.8 mmHg, *n* = 6) than virgins (7.5 ± 0.7 mmHg, *n* = 6) (*P* = 0.12). NE caused a dose-dependent increase in both MAP and MCFP in RB and aged-matched virgin control rats (Fig. 2, A and B). There was a higher pressor response to NE in the RB rats (ED50 = 3.6 ± 0.7 × 10−9 mol·kg⁻¹·min⁻¹, *n* = 6) than in the virgin rats (ED50 = 6.2 ± 0.4 × 10−9 mol·kg⁻¹·min⁻¹, *n* = 6), (*P* < 0.05). There was also a greater dose-related increase in MCFP in the RB rats (ED50 = 3.1 ± 0.5 × 10−9 mol·kg⁻¹·min⁻¹, *n* = 6) compared with the virgin rats (ED50 = 12.1 ± 2.7 × 10−9 mol·kg⁻¹·min⁻¹, *n* = 6), (*P* < 0.05).

Venous reactivity. NE caused a dose-dependent decrease in venous diameter in both RB and virgin rats (Fig. 3); however, the EC50 was lower in RB (2.68 ± 0.37 × 10−8 M, *n* = 5) than in age-matched virgin control rats (EC50: 4.67 ± 0.93 × 10−8 M, *n* = 8) (*P* < 0.05). There was no significant difference in the baseline diameter (RB: 563.87 ± 15.40 μm, *n* = 5, V: 568.6 ± 14.79 μm, *n* = 8, *P* = 0.83) or maximum response (RB: 129.80 ± 15.44 μm, *n* = 5, V: 127.37 ± 29.05 μm, *n* = 8, *P* = 0.87) of veins from RB and virgin rats.

Venous compliance and capacity. At physiological pressures (4–8 mmHg), the compliance (change in diameter/change in pressure) of veins was significantly lower in RB (29.3 ± 1.8 μm/mmHg, *n* = 6) than in the age-matched virgin rats (36.9 ± 1.3 μm/mmHg, *n* = 6) (*P* ≤ 0.05) (Fig. 4). Maximum capacity of the isolated mesenteric veins (12 mmHg) was lower in the RB rats (Fig. 4). Wall-to-lumen ratio of veins from RB (0.247 ± 0.02) was also significantly greater than that from virgin (0.203 ± 0.01) rats (*P* < 0.05).

**DISCUSSION**

We found no differences in baseline MAP, HR, or MCFP between RB and virgin rats. There was, however, a significantly greater pressor response to volume loading and to NE in the RB rats compared with the virgins, as well as an augmented increase in MCFP after infusion of NE. The data from the isolated vessels were consistent with our in vivo studies, namely, that mesenteric veins from RB rats were more reactive to NE and less compliant than those from virgin rats. This suggests that, under conditions of tonic autonomic outflow, total body venous tone would be higher in parous animals. Consistent with this was our finding that, even under basal conditions, blood volume was lower in the RB rats. Although it has been proposed that obesity can reduce the ratio between blood volume and body weight (38), our animals had been maintained on a reduced-calorie diet to prevent obesity (27). The difference in body weight between our parous and nulliparous animals was thus minimal and is unlikely to have contributed to the reduced blood volume and increased vascular reactivity in the RB rats.

Our finding that comparable volume loads induced a greater increase in blood pressure in parous than in virgin rats suggests that RB rats are less able to buffer increases in intravascular volume than are virgin rats. The increase in HR, rather than the anticipated reflex bradycardia, can probably be attributed to the Bainbridge reflex, whereby intravenous volume loading can increase HR (16). Although there was no significant difference between the groups, the tachycardia did tend to be greater in
the RB rats. Indeed, there was a significant increase in HR in the RB (at 3 min), but not in the virgin, rats. This again is consistent with their having an impaired ability to accommodate the volume load in the splanchnic circulation, so that there was a greater transient increase in cardiac preload.

The venous side of the splanchnic vascular bed plays a critical role in the homeostatic responses to changes in intravascular volume (39, 43). It is highly compliant, contains about 30% of total circulating blood, and is subject to reflex control of intraluminal volume (15, 32). Our attention was therefore directed to whether there was a difference in reactivity and compliance of the splanchnic (mesenteric) veins from RB and virgin rats. To this end, we measured MCFP during NE infusion in conscious unrestrained animals. MCFP is an index of total venous tone in the body and is an important determinant of venous return to the heart and cardiac output (14, 34). We found that RB rats had a potentiated MCFP response to NE infusion, suggesting that repeated pregnancy causes an increased vеноconstrictive response to sympathetic stimulation. This was confirmed in our in vitro study, where the NE EC50 of isolated mesenteric veins from RB rats was significantly lower than that for vessels from virgin rats. There was, however, no difference in the maximum constriction response to NE. Thus parity predominantly potentiates venous sensitivity

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to NE, while constrictive capacity is unaltered. These data suggest that, during sympathetic stimulation, the splanchnic vascular bed would exhibit higher venous tone in RB rats than in virgin rats, which would augment venous return and cause transient increases in cardiac preload (13, 34).

Whole body venous tone, as well as vascular reactivity of isolated veins, may be modulated by NO (9, 12, 25). There is also some evidence that NO may modulate arterial compliance (28). Given the evidence that repeated pregnancy reduces arterial endothelial NO (11, 36), the increased venous responsiveness of the RB rats to NE may probably also be attributed to reduced vascular NO bioavailability.

The in vitro venous responses to NE were potentiated in the parous rats. Although the question may arise as to how changes in vasoreactivity of isolated venous segments may relate to the control of overall splanchnic capacitance and tone, it should be pointed out that these results are consistent with our in vivo experiments showing an augmented NE-induced increase in MCFP in the RB rats. Furthermore, blood volume in the RB rats was significantly lower, which may also be attributed to higher sympathetic vascular tone (3). This concurrence between our in vitro and in vivo results lends credence to our contention that there is indeed a difference between the two groups with regard to reflex control of splanchnic capacitance.

One might have expected that baseline MCFP should have been elevated. However, the technical limitations of the protocol to measure MCFP may have precluded our being able to detect such a difference. The experiments had to be done just a few hours after surgery to minimize the risk of a thromboembolic event. However, at this time, resting sympathetic tone would undoubtedly have still been elevated in both the RB and virgin animals, which may have masked any potential difference in basal sympathetic control of splanchnic venous tone.

Studies of the changes in venous reactivity and compliance during pregnancy have been difficult to interpret. With regard to whole body compliance, there has been evidence for there being an increase (10), a decrease (24), or no change (7). Although Humphreys and Joels (22) reported a pregnancy-induced increase in MCFP, which was independent of sympathetic tone, they found total body compliance to be increased (22). Part of the difficulty in evaluating these results arises from the fact that both the splanchnic and peripheral vascular beds contribute to whole body compliance and that the degree to which each contributes probably varies according to the experimental conditions (anesthesia, species). Whereas compliance of the limb veins increases during pregnancy (42), mesenteric venous reactivity increases and compliance decreases (18, 20, 21). This reflects the very different functional roles of these vascular beds, the splanchnic circulation being important not only in delivering blood to the tissues, but also in controlling blood distribution and cardiac preload (13, 15, 32). Focusing as we did on the splanchnic circulation, we found mesenteric venous reactivity to be higher and compliance lower in parous than in virgin rats. This suggests that, even long after pregnancy, the splanchnic venous circulation retains many of the characteristics acquired during pregnancy (18, 20, 21).

Perspectives

The mechanisms underlying the effect of repeated pregnancies on venous tone and compliance are uncertain. It has been reported that pregnancy permanently alters levels of several reproductive hormones, which have potent vascular activity. For example, repeated pregnancy reduces plasma levels of estrogen (4). Through its genomic and nongenomic effects, estrogen increases the production of NO, attenuates the pressor response to vasoconstrictors, and increases vascular compliance; that is, it acts as a vasoprotective agent (1, 5, 37, 40, 44). Considering the abundant localization of estrogen receptors in the venous system (17), it is tempting to suggest that reduced estrogen (hormone/receptor) levels in parous animals might contribute to the enhanced MCFP and MAP responses and also to the reduced venous compliance, although we did not find any difference in plasma estrogen levels in our animals (11).

We have shown, in rats, that repeated pregnancy augments the pressor response to volume loading and to sympathetic stimulation. There is also an augmented increase in total body venous tone in response to $\alpha$-adrenergic receptor activation. This is due, at least in part, to changes in venous compliance and venous reactivity to NE in the splanchnic vascular bed. We propose that these changes would cause a reduction in the reservoir function of veins, thus compromising the ability of the capacitance venous system to accommodate volume overloads and to buffer changes in cardiac preload.

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