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# Remodeling of myometrial radial arteries in preeclampsia

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**Objective:** This study was undertaken to test for structural differences between myometrial radial arteries isolated from women having normal pregnancies and pregnancies complicated by preeclampsia and intrauterine growth restriction.

**Study design:** Pressure myography was used to study myometrial radial arteries obtained at cesarean section. With the use of a transilluminating system, lumen diameter, wall thickness, wall/lumen ratio, distensibility and stress-strain relationship were studied through a range of pressures. Arteries were then fixed in glutaraldehyde, embedded in resin, cross-sectioned, and studied in greater detail by light and electron microscopy.

**Results:** Pressure myography showed that arteries from women with preeclampsia had a reduced lumen diameter, thicker wall, and greater wall/lumen ratio compared with vessels isolated from women with normal pregnancy. Light microscopy indicated an identical media content remodeled around a smaller lumen. Electron microscopy indicated enlarged extracellular spaces in the media but no change in myocyte profile size or number. There was no clear evidence of structural changes in myometrial radial arteries isolated from women with intrauterine growth restriction compared with normal pregnancy. No differences in vessel distensibility or stress-strain relationships were detected in complicated pregnancies.

**Conclusion:** The changes observed in myometrial radial arteries isolated from women with preeclampsia are due to inward eutrophic remodeling. Alterations in these vessels may contribute to increased uterine vascular resistance in preeclampsia.



Preeclampsia and intrauterine growth restriction (IUGR) are conditions in which the placenta is believed to be poorly perfused. In support of this assertion, measurements reflecting uterine blood flow, using a variety of techniques, including radioisotope studies,[1,2] Doppler ultrasound,[3,4] and magnetic resonance imaging[5-7] have shown that flow is impaired in these conditions. The mechanisms that contribute to reduced uterine perfusion are not wholly understood. However, they are likely to reflect an alteration in either the structural or functional properties of the uteroplacental arterial vasculature.

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It has been proposed that placental blood flow is compromised in preeclampsia as a consequence of impaired endothelium-dependent vasorelaxatory responses of myometrial small arteries.[8] Whether this change reflects the primary reduction in placental blood flow, however, is a matter of some debate, because it has been proposed that the impairment of endothelial function is brought about by the release of a placentally derived circulating factor in response to placental underperfusion. In this model, the reduced placental perfusion occurs as a consequence of inadequate structural changes that occur within the spiral arteries.[9,10] In normal pregnancy, the processes of trophoblast invasion and placentation convert spiral arteries into low-pressure high-flow vessels and, in consequence, the major site of uterine vascular resistance is shifted upstream as well as to nonplacental bed sites. Thus, an important determinant of uterine vascular resistance in normal pregnancy is the diameter of maternal uterine radial arteries. To date, no studies have examined whether the structure of radial arteries differs between normal and compromised pregnancies.

In this study we have used physiologic and morphometric methodology[11] to determine whether there are structural differences in myometrial radial arteries isolated from women with normal pregnancy compared with pregnancies complicated by preeclampsia and IUGR.

## Material and methods

The Ethics Committee at Nottingham City Hospital gave approval for this work and all women who participated gave written informed consent. Women with essential hypertension and medical complications such as diabetes and renal disease were excluded from the study.

The definition of preeclampsia in this study conforms with that used by the International Society for the Study of Hypertension in Pregnancy. Preeclampsia was defined as the clinical syndrome in which a previously normotensive woman, has hypertension and proteinuria develop after the 20th week of pregnancy. Hypertension was defined as a blood pressure of at least 140/90 mm Hg on 2 or more occasions, separated by more than 4 hours. Proteinuria was defined as 2+ on urinalysis, or at least 300 mg/L or 500 mg per 24 hours in a 24-hour collection of urine in the absence of a urinary tract infection. Blood pressure and proteinuria needed to have returned to normal levels by the sixth week postpartum.[12]

Women with IUGR were selected on the basis of clinical or ultrasound suspicion of growth restriction. The individualized birth weight ratio was used as the final arbiter in defining growth restriction. The individualized birth weight ratio is the birth weight adjusted for maternal age, parity, ethnicity, gestation, and fetal sex.[13,14] The individualized birth weight ratio provides a better correlation with perinatal outcomes than birth weight for gestational age alone.[15] An infant with an individualized birth weight ratio of less than 10th percentile was considered growth restricted. For the purposes of this study, women recruited to the IUGR study group did not have preeclampsia, but 1 woman had pregnancy-induced hypertension.

Myometrial biopsy samples were obtained after delivery of the infant and placenta at cesarean section. A full thickness biopsy was obtained from the upper margin of the uterine incision within the lower uterine segment. These samples were placed in a container of calcium-free physiologic salt solution ($Ca^{2+}$-free PSS) and transported to the laboratory on ice.

The decidual and serosal portions of the myometrial sample were initially identified. The sample was pinned out in a dissecting dish such that the decidual portion was on the right and the serosal portion was on the left hand side. The sample was viewed under a light microscope and an artery was dissected free of surrounding connective tissue. Care was taken to ensure that the artery chosen was distant (at least 1 cm) from the decidua.

Myometrial arteries were mounted on a Halpern pressure-perfusion myograph[16]; segments of the vessels were secured between 2 cannulae and tied with a double strand (1 cm long) of surgical braided nylon suture. One cannula was closed and the other connected to a system containing $Ca^{2+}$-free PSS, which in turn was linked to a pressure-servo unit. This allowed the intraluminal pressure to be changed. The arteriograph was a 10-mL vessel chamber with an input and output channel to allow superfusion of $Ca^{2+}$-free PSS. The blood vessels were imaged with a video camera. The arteriograph in which the vessel was secured was connected to a 200-mL reservoir of $Ca^{2+}$-free PSS, which was bubbled with a 5% $CO_2$/95% $O_2$ gas mixture and circulated with a Masterflex pump (Cole-Parmer, London, UK) at a rate of 10 mL/min. This ensured that the arteriograph volume was exchanged once per minute. Temperature was maintained at 37°C.

Internal diameter and wall thickness measurements were made possible by transilluminating the vessel. These measurements were made through the pressure range of 5 to 100 mm Hg. At each pressure, 6 measurements of arterial wall thickness and 3 measurements of internal diameter were made along the length of the artery. When pressurized, arterial segments underwent some elongation. To compensate for any elongation, vessels were retracted with a micrometer to a length at which buckling was no longer apparent for each pressure. In general, very little adjustment was required. Once these measurements had been obtained, intraluminal pressure was set to the mean arterial pressure