Individual Common Carotid Artery Wall Layer Dimensions, but Not Carotid Intima–Media Thickness, Indicate Increased Cardiovascular Risk in Women With Preeclampsia
An Investigation Using Noninvasive High-frequency Ultrasound

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Background—Preeclampsia (PE) is associated with increased risk of cardiovascular disease later in life. Ultrasound assessment of the common carotid artery intima–media thickness (IMT) during or after PE has not indicated any increased cardiovascular risk.

Methods and Results—We used high-frequency ultrasound (22 MHz) to estimate the individual common carotid artery IMTs in 55 women at PE diagnosis and in 64 women with normal pregnancies at a similar stage. All were re-examined about 1 year postpartum. A thick intima, thin media, and high intima/media (I/M) ratio are signs of a less healthy artery wall. PE was associated with a significantly thicker mean common carotid artery intima, thinner media, and higher I/M ratio than in normal pregnancy (mean I/M difference, 0.21; 95% confidence interval, 0.17–0.25; \( P < 0.0001 \)). After adjustment for first trimester body mass index and mean arterial pressure, differences in intima thickness and I/M remained significant. About 1 year postpartum, these values had improved in both groups, but group differences remained significant (all adjusted \( P < 0.0001 \)). There were no significant differences in IMT between groups. In receiver-operating characteristic curve analysis, intima thickness and I/M were strongly predictive of prevalent PE (area under the curve, ≈0.95), whereas IMT was not (area under the curve, 0.49).

Conclusions—The arteries of women with PE were negatively affected during pregnancy and 1 year postpartum compared with women with normal pregnancies, indicating increased cardiovascular risk. Estimation of intima thickness and I/M ratio seem preferable to estimation of common carotid artery IMT in imaging cardiovascular risk in PE. Results from this pilot study warrant further confirmation. (Circ Cardiovasc Imaging. 2013;6:762-768.)

Key Words: cardiovascular diseases ■ carotid artery, common ■ carotid intima-media thickness ■ high-frequency ultrasound ■ intima/media ratio ■ preeclampsia ■ ultrasound

Preeclampsia (PE) is a pregnancy-specific syndrome, which affects 3% to 5% of all pregnancies.1 Worldwide PE is a leading cause of maternal and perinatal morbidity and mortality.2 The stresses and changes that occur during pregnancy can reveal the potential risks of chronic diseases,3 and PE is an independent risk factor for subsequent coronary heart disease and hypertension.4,5 Thus, ongoing or previous PE would be expected to be associated with signs of preclinical atherosclerosis. However, ultrasound assessment of the common carotid artery (CCA) intima–media thickness (IMT) has found no significant difference in the degree of atherosclerosis between women with ongoing or previous PE and women with normal pregnancies.6–8

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The CCA-IMT, estimated by 7 to 10 MHz ultrasound and covering the total thickness of the intima and media layers together, is the present gold standard for noninvasively assessing the degree of atherosclerosis.9 However, histomorphometry10 and intravascular high-frequency ultrasound11 have indicated that the intima increases in thickness and the media decreases in thickness with increasing age and atherosclerosis. Thus, a thick intima, thin media, and high intima/media (I/M) indicate a less healthy artery wall, as has consistently been shown using high-frequency noninvasive ultrasound to assess the individual artery wall layer dimensions.12–17 Individual assessment of each wall layer is preferable to assessment of the total CCA-IMT with regard to risk factors for cardiovascular disease (CVD) and prevalent CVD,17 effects of aging and menopausal hormone replacement,18 and conditions associated with increased risk of CVD.19–15

To our knowledge, no previous study has examined the individual artery wall layer dimensions in women with ongoing PE and their changes in the postpartum period. We used

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noninvasive high-frequency ultrasound to assess the absolute and relative dimensions of the individual artery wall layers in women with PE. Our hypothesis was that women with PE have a thicker arterial intima, a thinner media, and a higher I/M than women with normal pregnancies and that these differences remain about 1 year after pregnancy.

Methods
Fifty-five women diagnosed with PE and 64 women with normal pregnancies and pregnancy outcomes (controls) were recruited during 2007–2010. The participants came from urban and rural areas and had varying levels of education. Both nulliparous and parous women were included in the study. Women were not included if they had chronic hypertension, renal disease, or pregestational or gestational diabetes mellitus or if they were pregnant with >1 fetus. At the postpartum examination, about 1 year after delivery, 5 women in the PE group were pregnant again and did not want to participate. Among the controls, 4 women were pregnant, one did not want to participate, and one had moved from Sweden. Thus, 48 women in the PE group and 58 control women remained in the postpartum evaluation.

The women with PE were recruited at the antenatal clinic, Department of Obstetrics and Gynecology, University Hospital, Uppsala. PE was defined as new-onset hypertension (>140/90, observed on at least 2 separate occasions ≥26 hours apart) combined with proteinuria (>2 g on a dipstick or a 24-hour urine sample showing ≥300 mg albumin/24 h) after gestational week 20. Early onset PE was defined as a diagnosis of PE before gestational week 34, and late-onset PE was defined as a diagnosis of PE during gestational week 34 or later. PE was classified as severe when blood pressure was pronounced (systolic blood pressure, ≥160 mmHg and/or diastolic blood pressure [DBP], ≥110) and/or the proteinuria was massive (>5000 mg/24 h).

The controls were women with normal pregnancies and mean pregnancy duration at inclusion that was similar to that in the PE group (Table 1). Normal pregnancy was defined as a normotensive pregnancy resulting in term delivery (in gestational week 37 or later) with proteinuria (<0.5 g/24 h) after gestational week 20. Early onset PE was defined as a diagnosis of PE before gestational week 34, and late-onset PE was defined as a diagnosis of PE during gestational week 34 or later. PE was classified as severe when blood pressure was pronounced (systolic blood pressure, ≥160 mmHg and/or diastolic blood pressure [DBP], ≥110) and/or the proteinuria was massive (>5000 mg/24 h).

The controls were women with normal pregnancies and mean pregnancy duration at inclusion that was similar to that in the PE group (Table 1). Normal pregnancy was defined as a normotensive pregnancy resulting in term delivery (in gestational week 37 or later) with a normal weight infant (within ±2 SD of the mean birth weight for gestational age). Most of the women in the control group were included in our recent report and recruited during a routine visit at 2 of Uppsala County’s antenatal clinics; however, 8 women were recruited during a visit to the antenatal outpatient department at the University Hospital, Uppsala, because of perceived reduced fetal movements or suspected ruptured membranes, but everything was found normal and pregnancy was otherwise uncomplicated.

### Assessment During Pregnancy and at the Postpartum Period
Duration of pregnancy and gestational age were defined as completed weeks based on the second trimester routine ultrasound dating in pregnancy weeks 16 to 18. Data on age, reproductive history, smoking habits, and height were collected on the first visit. Maternal weight and calculation of body mass index (BMI, kg/m²) and systolic and diastolic blood pressure were monitored on all visits. Blood pressure was measured after about 15-minute rest, in the supine position, on the right upper arm, with an automated blood pressure equipment, Umedico, calf-size 12x35 cm, or otherwise a size appropriate for the arm circumference. Mean arterial pressure (MAP) is a better predictor of PE than systolic blood pressure and DBP and was calculated as DBP + ⅓ (systolic blood pressure – DBP). Data were collected from the delivery records about possible pregnancy-related complications, gestational week at delivery, mode of delivery, and birth weight of the infant. Small and large infants for their gestational age were defined as those with birth weights >2 SDs below or above the reference population’s mean birth weight for the gestational age.

At inclusion, a venous blood sample was collected from each woman. The samples were kept at room temperature for about half an hour before being centrifuged for 10 minutes at 2000g. The plasma samples were separated and stored at −70°C until levels of soluble fms-like tyrosine kinase 1 (sFlt1) and placental growth factor (PIGF) were analyzed using commercially available enzyme-linked immunosorbent assay kits (DY264 and DY321; R&D Systems, Minneapolis, MN). Absorbance was measured in a SpectraMax 250 (Molecular Devices, Sunnyvale, CA).

The study participants were examined twice, using high-frequency ultrasound of the left CCA. The first examination was performed during pregnancy in the women diagnosed with PE and in controls of a similar pregnancy stage. The second examination was performed about 1 year after delivery, when most of the women had ended lactation and started to menstruate. At the time of the second examination, all but 3 of the women who had had PE had restarted menstruation and all but 3 had stopped breastfeeding. Among the control women, all but 2 had restarted menstruation and all had stopped breastfeeding. The women who had not restarted menstruation were on contraceptives and, of the women who were still breastfeeding, all were breastfeeding partially and all had restarted menstruation.

### High-frequency Ultrasound of the Artery Wall
The left CCA wall layers were imaged using high-resolution ultrasound equipment fitted with a broad-band probe with 22-MHz center frequency (Collagenon; Minhorst Company, Meudt, Germany), as extensively described previously. In short, the artery wall layers were examined with the women sitting upright and looking straight ahead after they had rested for about 15 minutes. The transducer was applied at the point of maximal pulsation of the left CCA in front of the sternocleidomastoid muscle. The depth of penetration did not exceed 20 mm. The 3-layer image of the pulsating near wall was identified: 2 echo-dense zones (the adventitia and the intima) with an echo-lucent area (the media) in between followed by the echo-lucent artery lumen (Figure 1). Point estimates of the artery wall, not adjusted to the cardiac cycle, were obtained and about 20 point estimates were saved on a PC by one researcher (M.L.). The individual artery wall layer dimensions were measured offline for all participants by another researcher (T.A.), who was blinded with regard to study group and time of assessment. Means of about 10 technically acceptable measurements were calculated and used in the analysis. In our laboratory, the coefficient of variation was 3.9% for intima thickness and 3.4% for media thickness.

### Ethical Considerations
The study protocol was approved by the local Ethics Committee of the Medical Faculty of Uppsala University. Informed written consent was obtained from each woman included in the study.
Statistical Analysis
The results are presented as mean±SD. Differences in distributions were tested by χ² test. Between-group differences were tested using the Mann–Whitney U test and within-group differences using the Wilcoxon signed-rank test. Group differences for the main outcomes are also presented as mean differences (95% confidence intervals), in addition to the nonparametric testing. Between-group differences were also adjusted for differences in BMI and MAP in the first trimester using the nonparametric Willett’s residual method. In this method, for each artery wall layer dimension, a linear regression is fit, with the dimension as the dependent variable and MAP and BMI as independent variables. On the residuals obtained, a Mann–Whitney test is applied to compare the women with and without PE. Receiver-operating characteristic curve analysis was undertaken to illustrate and compare the discriminatory capacities of estimation of individual artery wall layer dimensions, CCA-IMT, and MAP in correctly predicting prevalent PE. Correlations between artery wall layer dimensions and sFlt1 and PlGF were assessed using the Spearman rank correlation test on the whole study material, justified by a strong overlap between study groups. The level of significance was set at a probability value ≤0.05. Statistical analysis was performed using the SPSS, version 20.0 (SPSS Inc., PASW statistics) for Windows software package.

Results
There were no significant differences in maternal age, gestational duration at inclusion, or smoking habits between the 2 study groups, although there were more nulliparous women among those with PE than controls (Table 1). Of the women with PE, 42% had early-onset PE, 69% had severe PE, and 86% were on antihypertensive medication (Table 1). Gestational duration at birth was on average 4 weeks shorter in the PE group than in controls (P<0.0001). Infants born to pre-eclamptic mothers had significantly lower birth weights than infants born to mothers with normal pregnancies, even after adjustment for gestational duration (Table 1). BMI, systolic blood pressure, DBP, and MAP were significantly higher in women with PE than in women with normal pregnancies in the first trimester, at inclusion, and at about 1 year postpartum (Table 2). In the first trimester (before diagnosis PE), none were on antihypertensive medication. Most of the women with antihypertensive medication (at diagnosis) could finish the treatment within few days and the rest within 6 weeks after delivery. None had antihypertensive medication at examination about 1 year postpartum.

At the time of PE diagnosis, women with PE had higher sFlt1 and lower PlGF than women with normal pregnancy (both P<0.001), and a higher I/M (P<0.0001) than control women of similar pregnancy duration. The differences in intima thickness and I/M ratio remained significant between study groups after adjustment for BMI and MAP in the first trimester (P<0.0001 for both) (Table 3). In parametric analysis, the mean difference in the I/M ratio between those with PE and controls was 0.21 (95% confidence interval, 0.17–0.25; P<0.0001). About 1 year postpartum, the intima thickness and I/M ratio had decreased (improved) in both PE (33% for both) and controls (27% for intima thickness and 25% for I/M ratio) (all P<0.0001), but the differences between study groups remained highly significant (P<0.0001 for both) (Table 3). CCA-IMT had decreased (improved) by 6% the PE group, mainly due to changes in intima thickness, and even less (by 1.5%) in controls, both not significant changes. The percentage differences between the groups were substantial, especially for intima thickness and I/M ratio. In contrast, combined IMT estimates differed by only a few percent, and not significantly, between PE and controls during pregnancy and at the postpartum evaluation.

Receiver-operating characteristic curve analysis revealed that both the estimates of carotid intima layer thickness and the calculated I/M strongly predicted prevalent PE. The area under the curve for the intima thickness was 0.98 and that for the I/M was 0.94, thus correctly differentiating women with prevalent PE at diagnosis (Figure 2A). One year postpartum, corresponding area under the curve was 0.95 and 0.90, respectively (Figure 2B). In contrast, estimates of the combined IMT were not useful for differentiating women with regard to prevalent PE, with area under the curve 0.49 during pregnancy and 0.46 about 1 year postpartum. Area under the curve values for MAP were 0.97 and 0.83, respectively (Figure 2A and 2B).

At diagnosis of PE, women with PE had higher sFlt1 and lower PlGF than women with normal pregnancy (both P<0.001).
In addition, both intima thickness and I/M ratio were significantly associated with sFlt1 ($r=0.51$ and $0.50$, respectively) and inversely with PI GF ($r=-0.43$ and $-0.46$; all $P<0.001$), whereas CCA-IMT showed opposite and not significant associations.

Among the women with PE, none of the artery wall layer dimensions differed significantly between early-onset and late-onset PE, between mild/moderate and severe PE or with regard to antihypertensive therapy. Furthermore, artery wall layer dimensions did not differ significantly between nulliparous and parous women with either PE or normal pregnancies (data not shown). However, primipara, compared with multipara, had numerically, but not statistically significantly, thicker intima ($P=0.081$), thinner media, and higher I/M ratio. Similarly, women with early onset preeclampsia compared with late onset preeclampsia I/M ratio was numerically higher (0.43 versus 0.39) but not significantly so ($P=0.14$).

**Discussion**

We found substantially higher values for CCA intima thickness and I/M in pregnant women at the time of diagnosis of PE, compared with those in women with normal pregnancies of similar stage. About 1 year after delivery, these dimensions had significantly decreased in both groups, more so in the PE group, but were still significantly higher in women with previous PE. We interpret these data as follows. The artery walls in women with PE were substantially negatively affected at the time of PE diagnosis. The condition improved after delivery, but, after about 1 year, women with a history of PE still had negatively affected artery walls compared with women with normal pregnancies. Receiver-operating characteristic analysis using intima thickness or I/M strongly differentiated between subjects with and without prevalent PE, with $c$ values of over 90%. At diagnosis of PE, we found significantly higher sFlt1 and lower PI GF than in controls, consistent with previous studies. In addition, both intima thickness and I/M ratio, but not CCA-IMT, associated logically and highly significantly to serum levels of sFlt1 and PI GF, suggesting a true association between artery wall layer dimensions and PE. Our interpretation of the changes in artery wall layer dimensions in women with PE is based on previous results from histomorphometry, as well as intravascular high-frequency ultrasound results in relation to atherosclerosis. This interpretation is also supported by the results of our previous studies, using the same technology, with regard to cardiovascular risk factors and prevalent CVD and the effects of aging and menopausal hormone replacement. Our interpretation of the data is also in line with results from premenopausal women with a known or suspected increased risk of CVD, for example, those with systemic lupus erythematosus (SLE), after recurrent major depression, and after bone marrow transplantation in adolescents.

The proportional differences in artery wall layer dimensions between study groups during pregnancy and in the changes from pregnancy to the examination about 1 year postpartum...
were more pronounced for intima thickness and I/M than for media thickness. This is logical considering the low mean age of the study population and since inflammation and recruitment of inflammatory cells to the intima occur early in the atherosclerotic process, primarily resulting in intimal thickening. However, results for both intima thickness and I/M are presented because I/M provides strong images of age-related changes, the effects of interventions such as hormone replacement therapy and the effects on the artery wall of conditions characterized by inflammation, for example, prevalent CVD and SLE. The advantage of using separate estimates for each individual artery wall layer to image cardiovascular risk in premenopausal women is apparent from our report on women with SLE. Assessment of combined IMT, both in this study and in a well-done study by Roman et al indicated paradoxically healthier artery walls in women with SLE than in controls. In contrast, using the suggested method, women with SLE had artery wall images similar to those of postmenopausal women who were 30 years older. In 70-year-old men and women, the suggested method strongly discriminated with regard to prevalent CVD, whereas CCA-IMT did not.

Although we did not assess artery wall layer thickness before pregnancy for comparison in these women, when historical data using the same technology were evaluated, the artery wall layer dimensions in women with PE were approaching those in healthy 70-year-old postmenopausal women. One year postpartum, the artery wall layer dimensions had improved in women with PE, but they were still more negatively affected than those in the controls of this study and than those in healthy premenopausal women who were almost 10 years older, as evaluated in a recent report using the same technology. These findings suggest an increased risk of CVD later in life for women with PE.

In accordance with this, in a recent meta-analysis by Bellamy et al based on 25 prospective and retrospective cohort studies, women with previous PE had an increased risk of developing ischemic heart disease (relative risk 2.16) and hypertension (relative risk 3.70) compared with women with previous normal pregnancies. In an another meta-analysis, McDonald et al found similar results indicating an increased risk of developing CVD (relative risk 2.33) in women with a history of PE compared with women with uncomplicated pregnancies. Our findings of less healthy individual CCA wall layer dimensions in women with PE, apparent both during pregnancy and about 1 year postpartum, are totally in agreement with the documented increased risk of later CVD in women with PE.

Endothelial dysfunction is a key factor in the early pathogenesis of atherosclerosis. PE is a systemic vascular disorder that begins in the placenta and finally affects the maternal endothelium. Endothelial dysfunction with peripheral vasoconstriction and decreased arterial compliance contribute to development of hypertension and glomerular endotheliosis resulting in proteinuria. Chambers et al showed that women with a history of PE had impaired endothelial function with reduced endothelium-dependent dilatation at 3 months and up to at least 3 years postpartum, compared with women with previous uncomplicated pregnancies.

As women with PE have an increased risk of CVD later in life, those with current or previous PE would be expected to show signs of preclinical atherosclerosis. These signs were clearly shown in our study using estimation of the thickness of individual artery wall layers. In contrast, our estimates of combined IMT, which is the gold standard for noninvasive assessment of the degree of atherosclerosis, showed only minute insignificant differences between study groups during pregnancy or postpartum and did not differentiate women with regard to prevalent PE. Similarly, the few previous studies addressing the use of conventional CCA-IMT have shown no convincing indications of increased CVD risk in women with ongoing or previous PE. When Blaauw et al investigated a group of women with previous early-onset PE, about 6 months postpartum, there were no significant differences in CCA-IMT between women with and without previous PE. Similarly, Haukkamaa et al found no significant differences in CCA-IMT between women with and without previous PE. Thus, studies specifically addressing PE did not find any significant difference in CCA-IMT between women with PE and women with normal pregnancy, which is totally in accordance with our findings for combined IMT.

Major strengths of our study included the estimation of the separate artery wall layer dimensions, a method that seems preferable to CCA-IMT imaging in patients with known or suspected arterial aging, and results from both during and after pregnancy, which permitted analysis of postpartum changes. Further, all ultrasound examinations were performed...
by one researcher (M.L.) and all ultrasound images were ana-
alyzed by another researcher (T.A.), blinded with respect to 
study group affiliation. Women with PE were admitted con-
secutively at Uppsala University Hospital, a referral hospital. 
Thus, the proportion of more severe PE might be higher than 
normal among all women with PE.

One limitation of our study is that we had no prepregnancy 
data about artery wall layer dimensions in the study par-
ticipants. Therefore, any potential prepregnancy changes in 
the arteries contributing to development of PE could not be 
addressed in this study. However, we did compare our data 
with results from our previous studies using the same tech-
ology. Another limitation is the relatively small sample size, 
not with regard to the logical and consistent statistically sig-
nificant findings, but with the associated potential risk of type 
2 error. The small sample size might thus contribute to the 
finding of no significant differences between early- and late-
onset PE, between severe and less severe PE, and with regard 
to antihypertensive therapy and parity. Further, it would have 
been preferable to have an additional control group, to evalu-
ate whether changes are similar in, for example, gestational 
hypertension or more specific for PE.

Our findings of improved artery wall layer dimensions 1 year 
postpartum compared with during pregnancy indicate that 
pregnancy per se might have a negative effect on the artery 
wall image, as suggested in our recent report.12 It is uncertain 
whether the differences in artery wall layer dimensions 
between PE and normal pregnancy are an effect of PE only or 
whether affected artery walls exist already before pregnancy 
in women who later develop PE. However, this is a totally 
different question that needs to be addressed in further stud-
ies. This study presents a noninvasive ultrasound method that 
strongly discriminated women with and without prevalent PE 
and, in contrast to CCA-IMT, indicated the known increased 
cardiovascular risk in women with PE.

Conclusions

Using high-frequency ultrasound to measure the individ-
ual artery wall layer dimensions, we found substantially affected 
arteries during and after preeclamptic pregnancy. Our findings 
are in total agreement with the documented increased risk of 
CVD later in life in women with a history of PE,15,29,30 whereas 
CCA-IMT in this study and previous reports did not indicate 
any increased risk of CVD in women with PE. Because of the 
moderate sample size, this study should be perceived as a pilot 
study, and further studies with larger sample size are highly 
warranted. After further evaluation, the method might have the 
potential to become a tool in stratifying women with PE with 
regard to cardiovascular risk, enabling early intervention to 
reduce their cardiovascular-related morbidity and mortality.

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Assessment of the individual thicknesses of the intima and media layers and calculation of the intima/media ratio seems to provide an image of early atherosclerosis and could potentially be useful for stratifying women with preeclampsia with regard to cardiovascular risk. If so, the method might potentially become an important tool in reducing cardiovascular disease–related morbidity and mortality in women with a history of preeclampsia through early diagnosis and intervention. The method of calculating intima/media ratio could also be a useful tool for identifying individuals, both men and women, who are at increased risk of cardiovascular disease, for example, individuals with essential hypertension, diabetes mellitus, and systemic lupus erythematosus, to image vascular aging and preclinical atherosclerosis, enabling early intervention and potential reduction in their long-term cardiovascular risk. However, further studies are required to explore the potential of this method.
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