SEMINARS IN
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Cardiovascular Changes in Preeclampsia

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The cardiovascular system undergoes a host of changes in association with the development of preeclampsia, which ultimately lead to the classic low cardiac output–high systemic vascular resistant state. A newer hypothesis suggests that exaggeration of the normal for pregnancy hyperdynamic, low-resistance state commencing in early gestation is responsible for the genesis of the clinically apparent vasoconstrictive disease in late pregnancy. Such events may also lead to the vascular damage that persists into later life. In preeclampsia, cardiac contractility is preserved but both steady and pulsatile arterial load are increased inappropriately, failing to decrease as would occur in normal pregnancy, involving both conduit and small vessels. Abnormal adaptive mechanisms may be secondary to changes in vascular tone or vascular wall elements, and may have future implications for a woman later in life.

KEYWORDS arterial compliance, cardiovascular function, pulsatile arterial flow, preeclampsia, hemodynamics, vascular properties

Preeclampsia, defined by increased blood pressure and proteinuria, is a systemic disorder that in its more severe forms may be associated with serious morbidity and even death. Effects of the disease on the cardiovascular system may be integral to these observations, although reports documenting such effects can be contradictory. This review summarizes knowledge regarding cardiac performance and vascular changes in preeclampsia, focusing on recent progress made possible by advances in noninvasive technology. A brief summary of the normal physiologic cardiovascular changes in pregnancy, however, must precede any discussion of the pathophysiologic state.

Hemodynamics and Cardiac Function in Normal Pregnancy

Cardiac output increases and systemic vascular resistance (SVR) decreases early in gestation, but the latter is greater, triggering a decrease in mean arterial pressure that nadirs at 16 to 20 weeks gestation. Mean arterial pressure then gradually increases and near term may reach preconception levels.[1-4] The increase in cardiac output, noted as early as week 5, peaks as much as 50% over nonpregnant levels by midgestation, usually persisting to term, although some investigators have recorded decrements. The changes in cardiac output are caused by a 20% increase in both stroke volume and heart rate. Intravascular volume also increases by approximately 40%. Left ventricular mass and end-diastolic dimension as well as the left ventricular outflow tract have been noted, although not by all investigators, to increase.[2-11] Left ventricular contractility has been assessed by load-dependent methods, with great variability in results,[3,11] as well as load-independent designs that tend to provide consistent findings. This is discussed in detail later.[4,7,10,12]

Review of the literature also reveals a number of methodologic problems that complicate adequate characterization of normal and pathologic cardiovascular performance during pregnancy. Such problems must be recognized and addressed if we are to assess effects of preeclampsia on the cardiovascular system. For example, the use of traditional ejection-phase indices of left ventricular performance are a problem in that these indices are unable to distinguish alterations in contractility from changes in ventricular load.[7,13-15] Additionally, administration of volume-expanding fluids or vasoactive therapy before acquisition of data, acquisition during active labor, or with inconsistent maternal posture all will influence cardiovascular parameters. Finally, the inclusion of patients with underlying medical disorders such as diabetes or renal disease will complicate the interpretation of data.[7,14]

Hemodynamics and Cardiac Function in Preeclampsia

The traditional characterization of preeclampsia is one of decreased intravascular volume and arteriolar vasospasm.

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Table 1 Hemodynamic Profile in Untreated and Treated Preeclamptic Patients and Normotensive Pregnant Women

	Preeclamptic Patients, Untreated (N = 87)	P*	Normotensive Controls (N = 10)	P†	Preeclamptic Patients, Treated (N = 47)
Mean intra-arterial pressure (mm Hg)	125 (92–156)	<.001	83 (81–29)	<.001	120 (80–154)‡
Cardiac index (L × min^{-1} × m^{-2})	3.3 (2.0–5.3)	<.001	4.2 (3.5–4.6)	NS	4.3 (2.4–7.6)‡
SVR index (dyne × sec × cm^{-5} × m^2)	3,003 (1,771–5,225)	<.001	1,560 (1,430–2,019)	<.005	2,212 (1,057–3,688)‡
Pulmonary capillary wedge pressure (mm Hg)	7 (−1 to 20)	NS	5 (1–8)	<.05	7 (0–25)

NOTE. Values given are median (range).
Abbreviation: NS, not significant.
Reprinted with permission from Visser and Wallenburg.[17]
*Differences between untreated preeclamptic patients and normotensive controls.
†Differences between pharmacologically treated preeclamptic patients and normotensive controls.
‡P < .05 versus untreated nulliparous patients.

The normal pregnant physiologic state of high cardiac output coupled with a low-resistance systemic circulation shifts to the opposite extreme of a low-output, high-resistance state with the acute onset of preeclampsia.[14,16] This was shown best by Visser and Wallenburg.[17] These investigators studied a large cohort of untreated and treated severe nulliparous preeclamptic patients (n = 87 and 47, respectively), nulliparas, presenting before gestational week 34 who were selected carefully by strict diagnostic criteria including diastolic pressure of 100 mm Hg measured twice 4 hours apart, proteinuria levels of 0.5 g/L or greater, onset at 20 weeks of gestation or later, and complete resolution postpartum. Hemodynamics were evaluated by using a pulmonary artery catheter and thermodilution technique, and the results were compared with those of 10 normotensive controls similarly studied.

Remarkably consistent hemodynamics were obtained in the untreated preeclamptic women, a low-output–high-resistance state compared with normal pregnancy, associated with normal pulmonary capillary wedge pressure (Table 1). This contrasted the observations in the treated preeclamptic patients whose results were quite heterogeneous, although in general they showed cardiac indices and SVRs more comparable with normal pregnancy. This study, confirming a preliminary report,[18] shows the pitfall that these and other investigators have encountered when trying to separate observations on cardiovascular alterations in preeclampsia from those caused by interventions such as fluid, magnesium, and antihypertensive drug administration. These observations underscore that without the presence of such confounding variables, preeclampsia is characterized by substantial decrements in cardiac output and marked increments in SVR.

These findings have been verified by Lang et al[7] by using noninvasive echocardiographic techniques. Ten carefully selected preeclamptic patients displayed decreased cardiac output and higher SVR compared with 10 normotensive controls, both groups were studied near term. No differences were noted when both groups were restudied 1 month postpartum.[7]

More recently, the earlier-described traditional view that preeclampsia is a vasoconstrictive disorder, starting insidiously long before overt disease, has been challenged. Easterling et al[19] and Bosio et al[20] have espoused a cross-over hypothesis in which the pathophysiology of preeclampsia is similar to that of essential hypertension, having an early hyperdynamic phase characterized by increased cardiac output with systemic resistance initially decreasing to protect against the appearance of high blood pressure. Only when this peripheral autoregulation fails do increases in SVR and eventually decreases in cardiac output occur. The Easterling et al[19] and Bosio et al[20] groups see preeclampsia as a recapitulation of this usually gradual process over the 9 months of pregnancy, and the hallmarks of this disorder include an excessive increase in cardiac output beyond that observed in normal gestation, with an initial protective exaggeration of the normal decrease in SVR. Then there is a cross-over to a high resistance state that causes the decreased cardiac output, all occurring late in gestation when preeclampsia becomes clinically apparent. In the study by Easterling et al,[19] serial data were collected from 179 nulliparous gravidas by using noninvasive Doppler techniques, and 9 of this cohort subsequently developed preeclampsia. Mean arterial blood pressure and cardiac output both were increased early in gestation, while SVR remained low in those destined to become preeclamptic. The investigators also noted that blood pressure in those destined to develop preeclampsia, although initially normal, was always higher compared with those with normotensive gestations, the difference owing to their higher cardiac outputs.

There were many problems with the study of Easterling et al[19] that cannot be detailed here, including a large drop-out rate, a limited number of patients developing preeclampsia, and 7 of 9 who had but mild disease. The mean gestational age at delivery was 39.4 weeks, and the neonates' birthweights were similar to those of the normotensive group. Finally, the preeclamptic group was approximately 12 kg heavier than the normal group, a fact that could contribute to their higher cardiac output and lower SVR.[21]

The study by Bosio et al,[20] however, is more convincing. They, too, used a serial design using noninvasive Doppler techniques. Their study had better compliance, more pre-

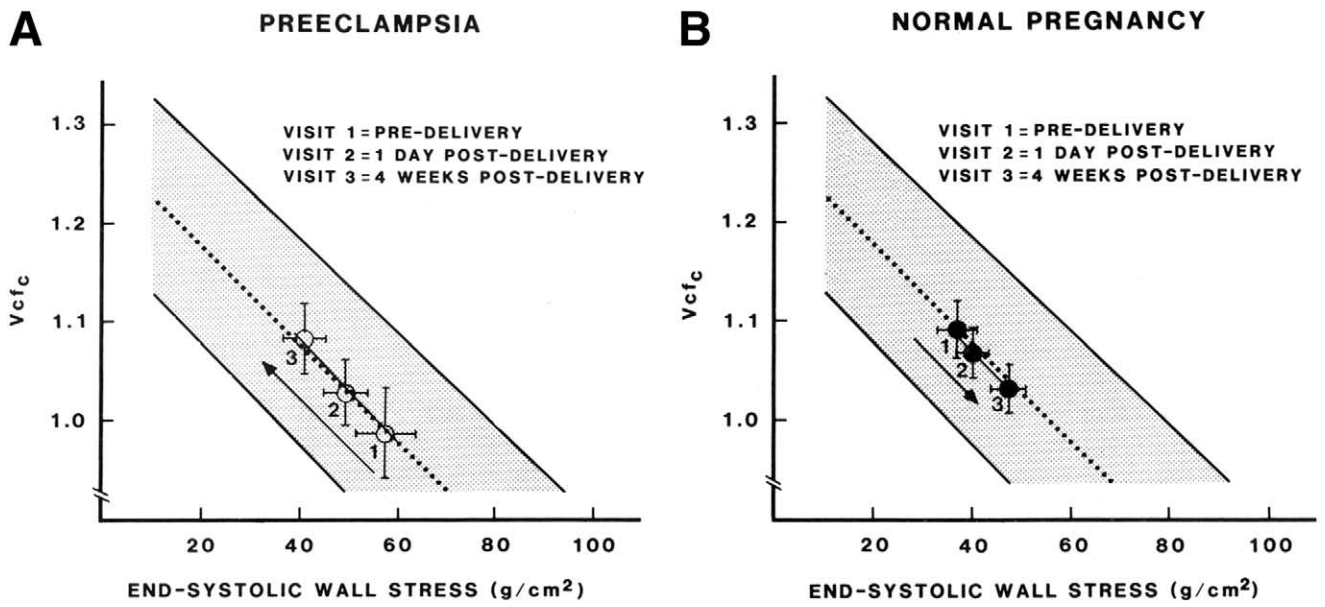

Figure 1 (A) Average end-systolic wall stress (σ_{es})-rate-corrected velocity of fiber shortening (Vcf_c) obtained in patients with preeclampsia before delivery, 1 day after delivery, and 4 weeks after delivery. From visit 1 to visit 3, data points shifted leftward and upward (arrow) but still fell on the mean contractility line, indicating decreased afterload without changes in contractility. (B) Average end-systolic wall stress (σ_{es})-rate-corrected velocity of fiber shortening (Vcf_c) obtained in normotensive pregnant control subjects before delivery, 1 day after delivery, and 4 weeks after delivery. From visit 1 to visit 3, data points shifted rightward and downward (arrow) but still fell on the mean contractility line, indicating increased afterload without changes in contractility. Visit 1, predelivery; visit 2, 1 day after delivery; visit 3, 4 weeks after delivery. Reprinted with permission from Lang et al.[7]

eclamptic patients, and less weight differential. Again, cardiac output was increased early in the pregnancies of women destined to develop preeclampsia. Late in the clinical phase of the disease, however, the SVR increased markedly and cardiac output decreased and their findings resembled those of the untreated preeclamptic patients described by Visser and Wallenburg[17] and Groenendijk et al,[18] with markedly decreased cardiac output and increased SVR. Postpartum, the cardiac output and resistance returned to values similar to those of the nonpreeclamptic group.[20] It should be noted here that although the cross-over postulate is of interest, more studies are needed to confirm it, as are explanations of how this hypothesis is compatible with other findings in preeclamptic patients. These include early evidence of vasoconstrictive phenomena such as increased pressor responsiveness, the early detection of circulating proteins harmful to the endothelium (see article, "Angiogenic Imbalance in the Pathophysiology of Preeclampsia: Newer Insights", by Bdolah et al in this issue), and decrements in intravascular volume, such events detected weeks to months before overt disease.

Left Ventricular Mechanics in Preeclampsia

In an attempt to dissect the effects of preeclampsia on left ventricular function from the confounders discussed earlier, Lang et al[7] used a load-independent analysis of left ventricular contractility to investigate the heart in preeclampsia. Previous investigators have reported conflicting results, but all had used traditional ejection-phase indices as measures of left ventricular contractility.[7,13,15] The relationship between left ventricular end-systolic wall stress and rate-corrected velocity of fiber shortening is a sensitive index of left ventricular contractility that is independent of preload and heart rate, while incorporating afterload into the analysis.[22] A preeclamptic group was selected carefully and studied before antihypertensive therapy (although magnesium sulfate had been administered) and compared with normal controls. Figure 1 shows end-systolic wall stress rate–corrected velocity of fiber-shortening data points for preeclamptic (Fig 7A) and normal pregnant women (Fig 7B) compared with normal controls (mean line, shaded areas).[7] Ventricular performance was evaluated by comparing individual patient data points with a mean contractility line and its confidence intervals (shaded area) in the graph. Points 1, 2, and 3 in Figure 7A represent data obtained before induction or cesarean delivery, 1 day after delivery while still hypertensive but no longer on magnesium sulfate, and 4 weeks postpartum when blood pressures had normalized. The values were similar to those of the normotensive controls obtained at the same 3 time points, shown in Figure 7B. All data points for the preeclamptic patients (Fig 7A) fell on or close to the mean contractility line, although by 4 weeks postpartum there was a leftward and upward shift indicating decreased afterload while maintaining normal contractility. The normal control group also maintained normal contractility, although by 4 weeks postpartum a rightward and downward shift occurred,

indicating an increase in afterload. Thus, Lang et al[7] showed that in preeclamptic women the left ventricular myocardial contractility, as defined by invariant left ventricular stress rate–corrected velocity of circumferential fiber shortening, was unchanged and similar to the observations of normal contractility in the normal pregnancy group. Of some concern, however, was that the mean contractility line in this study was derived from nonpregnant patients, but of greater importance is the near-identical behavior of the hearts of both diseased and normal pregnant women.

That myocardial contractility is unchanged in normal pregnancy was verified further by our group in a longitudinal study,[4] and Simmons et al[12] recently showed similar myocardial contractility in 15 preeclamptic patients compared with 44 normal pregnant controls. Only Mone et al,[10] by using the same noninvasive methodology, observed an increase in contractility in normal pregnancy, although this was associated with a reduction in left ventricular afterload. Additionally, they used the second heart sound as a marker of end systole, which actually occurs shortly after the maximum posterior motion of the septum, and possibly affected their results. Preeclamptic patients were not studied. Thus, the use of sophisticated noninvasive techniques by others as well as by us leads to the conclusion that myocardial contractility is preserved in both normal and preeclamptic gestations.

Systemic Arterial Circulation in Preeclampsia

The arterial circulation is characterized by a dynamic interaction of blood flow and vascular components, and undergoes profound changes in normal pregnancy.[4] Generalized vasodilation is noted as early as 5 weeks gestation,[1] with a concomitant increase in cardiac output and intravascular volume and no increase in arterial blood pressure. One should note that in much of the literature, the arterial system is viewed in a simplistic manner, using total vascular resistance (TVR), the opposition to steady blood flow, as the major parameter describing the systemic arterial circulation. However, because the heart is ejecting blood in a pulsatile fashion into a distensible system, more complex concepts are required to describe both the normal and abnormal physiology of the heart and circulation, especially in pregnancy with its hormonal changes, which may affect vessel wall components, altering vascular tone and leading to possible remodeling in certain vascular beds. Specifically, components other than TVR are required to describe the pulsatile aspects of the arterial load adequately, which is determined by properties such as vessel geometry, wall composition and smooth muscle tone, the architectural network of vessels, as well as the mechanical properties of blood.[23] The input impedance spectrum (ie, impedance as a function of frequency) is a comprehensive characterization of arterial load. Impedance at zero frequency is identical to TVR. Because the rest of the input impedance spectrum is a complicated representation (a set of frequency-dependent complex numbers), simplified indices often are used to characterize pulsatile arterial load. Global

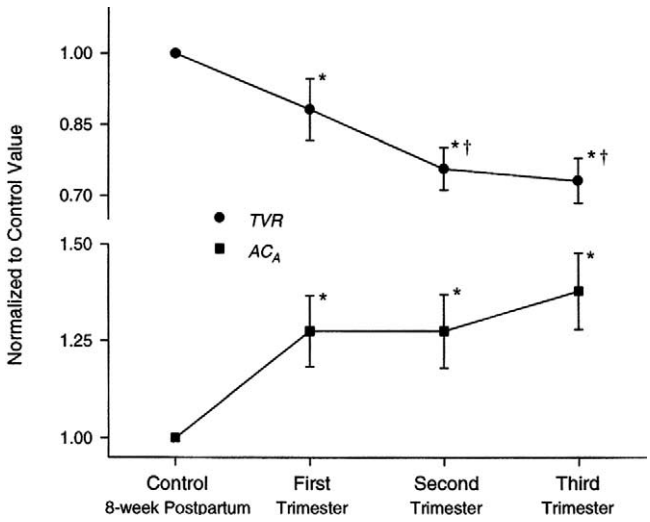

Figure 2 Temporal changes in AC and TVR during normal pregnancy. Data are normalized to 8-week postpartum control values (mean ± standard error of the mean; $*P <$ first, second, or third trimester versus 8-week postpartum control; $+P < .05$, second or third versus first trimester). ●, TCR; ■, AC_A. Reprinted with permission from Poppas et al.[4]

arterial compliance (AC), magnitude of input impedance at the first harmonic (Z_1), characteristic impedance (Zc), and reflection index are examples of these simplified indices. Global arterial compliance is a measure of the elasticity or reservoir-like properties of the arteries. Z_1 depends on TVR and AC and thus is determined by the entire circulation (both small and large vessels). In contrast, Zc is a local property (ie, belonging to the site of pressure and flow measurement) determined by local vessel wall stiffness and geometric properties. The reflection index is a measure of the degree of wave reflections in the arterial system. Understanding the interactions of these components helps one comprehend the remarkable intact performance of the cardiovascular system during normal gestation, and allows extension of these observations to disease states such as preeclampsia.[23]

We performed a serial study on 14 normal pregnant women who underwent noninvasive cardiac testing during each trimester and 8 weeks postpartum, the results showing that AC increases approximately 30% in the first trimester, and remains increased thereafter. This increase is accompanied temporally by the expected decrease in SVR (Fig 2).[4] Such an increase in vessel distensibility might be secondary to vascular remodeling changes or reduced smooth muscle tone, documented to occur very early in pregnancy.[2,3] Both measures of impedance, Z_1 and Zc, decreased throughout pregnancy, although only the former decreased significantly, resulting in a reduction of the magnitude of arterial wave reflections. Interestingly, Mone et al,[10] in a similar investigation, confirmed that Zc was decreased significantly in a larger cohort of gravidas. The aortic pressure and flow waveform data in our investigation were subjected to a model-based analysis revealing that wave reflections at the aorta are delayed and AC increases for both conduit and peripheral vessels; furthermore, a decrease in TVR alone is inadequate to

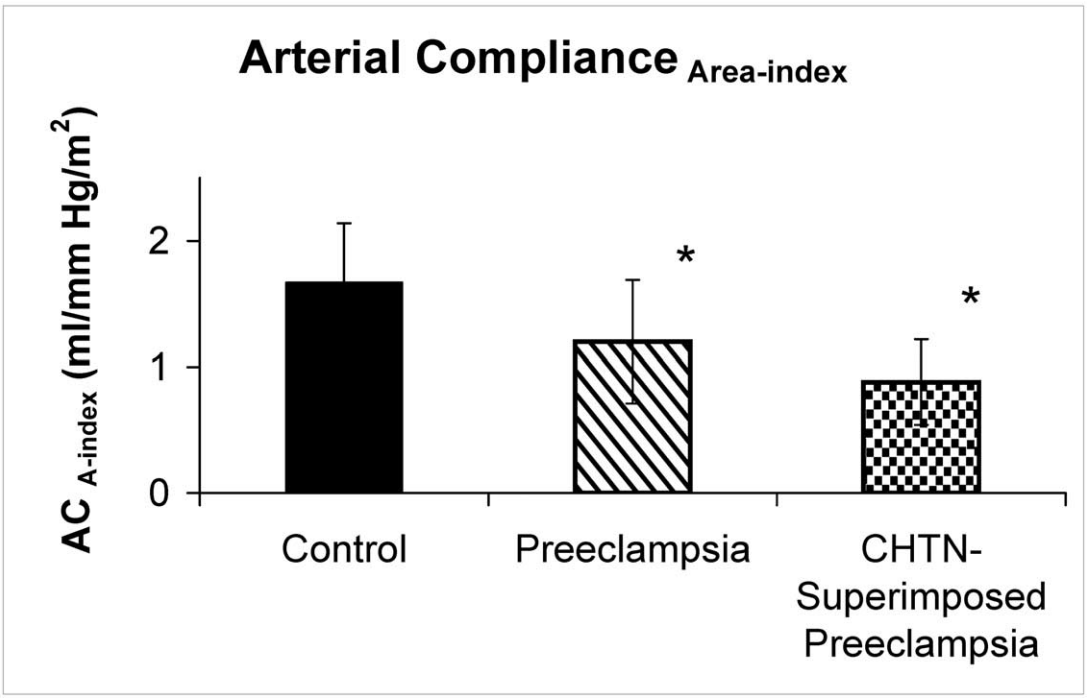

Figure 3 Global arterial compliance index, a measure of the elasticity component of the entire system, both conduit and peripheral vessels, is depicted for the 3 study groups: normal controls solid bar, preeclamptic patients striped bar, chronic hypertension with superimposed preeclampsia checked bar. $*P < .05$ compared with normal control group. (Figure constructed with data from reference 24.)

reproduce the experimental findings, requiring concomitant alterations in both arterial compliance and wave propagation properties. Thus, a generalized decrease in vascular tone is most likely responsible for changes in pulsatile arterial load in normal pregnancy.[4]

These striking adaptive responses are important in that increased AC accommodates the increased intravascular volume of gestation, allowing the mean arterial pressure to remain low. Furthermore, it counterbalances the reduced TVR and promotes an efficient left-ventricular-to-arterial system mechanical energy transfer and maintains perfusion of vital organs during decreased TVR.

We also applied this approach to study cardiovascular alterations in preeclamptic gravidas, hypothesizing that failure of the pulsatile arterial load to adapt may contribute to the pathophysiology of this disease state.[24] To this end we designed a cross-sectional study that included preeclamptics, chronic hypertensives with superimposed preeclampsia, and normotensive gravidas with preterm labor. All of these women were receiving magnesium sulfate, either to prevent eclampsia, or in the case of the normotensive gravidas, tocolysis. Additional control groups included normotensive gravidas receiving epidural anesthesia and normal parturients, neither receiving magnesium nor epidural analgesia. We observed, as expected, the steady component of arterial load, TVR, was significantly greater in both preeclamptic groups and that global arterial compliance was significantly lower in the pure preeclamptic group, and more so in those with superimposed preeclampsia, indicating the effects of the disease state on the entire arterial system (Fig 3). The impedance measurement that incorporates both large and small vessels, Z_1, was significantly elevated in both study groups (Fig 4); characteristic impedance, Zc, was greater in both hypertensive groups, though not significantly. The index of wave reflection within the arterial tree, RI, was increased in the preeclampsia group, though not significantly, and even more so in the gravidas with superimposed preeclampsia.[24]

By dissecting components of the arterial load using these techniques and modeling in hypertensive disorders of pregnancy we can isolate several factors that affect pulsatile arterial flow. In the case of the pure preeclamptic patients there appears to be a relatively higher arteriolar tone affecting both the central conduit vessels as well as the arterioles in the periphery. Previously we have noted that in normal gestation increased vascular distensibility of the arterial system may result from reduced smooth muscle tone; although we cannot discount structural remodeling of vascular wall elements.[4] It is plausible that increased smooth muscle tone in preeclampsia mainly is responsible for our results. Whether the time course for vascular wall remodeling is sufficient in this disease state is unknown.

More recently Elvan-Taspinar et al[25] studied central hemodynamics in normal, hypertensive, and preeclamptic pregnancies by using noninvasive applanation tonometry to measure aortic stiffness and aortic pressure waveforms. Briefly, pulse wave velocity was measured between the carotid and femoral arteries and an increase in velocity was indicative of increased stiffness of the corresponding vascular section. Aortic waveforms and central pressure, as well as a measure of cardiac supply and demand, then were derived by using a

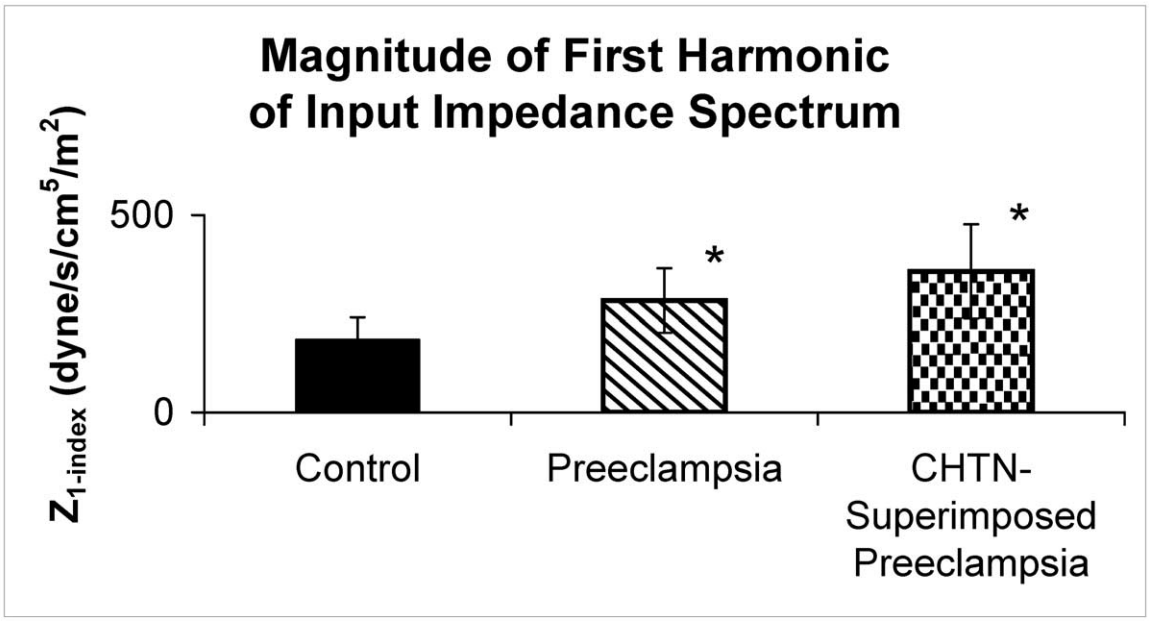

Figure 4 The magnitude of the first harmonic of the input impedance spectrum index, representing impedance properties of both large and small vessels, is depicted for the 3 study groups: normal controls solid bar, preeclamptic patients striped bar, chronic hypertension with superimposed preeclampsia checked bar. *$P < .05$ compared with normal control group.

transfer function. This group showed that aortic stiffness and central pressures were greater in hypertensive gravidas and even more so in preeclamptic patients, while the ratio of cardiac supply and demand remained intact, lending support to the idea that increased blood pressures are an important determinant of decreased arterial compliance.[26,27]

Vascular reactivity has been noted to be increased weeks to months before the development of preeclampsia,[28] and factors influencing increased smooth muscle tone may be responsible for such observations.[24,25] To this end, Schobel et al[29] studied postganglionic sympathetic nerve activity in carefully defined preeclamptic patients, comparing them with normal gravidas, and nonpregnant normal and hypertensive women. By using intraneural microelectrodes inserted into blood vessels of skeletal muscle, they showed that baseline sympathetic nerve firing was 3 times higher in the preeclamptic group compared with all 3 control groups. Postpartum sympathetic hyperactivity decreased concomitantly with blood pressure in the study group 1 to 3 months postpartum. The sympathetic hyperactivity correlated not only with increased blood pressure and TVR in this work, but also with the decreased arterial compliance and increased impedances noted in our work.[24] However, increased sympathetic vasoconstrictor activity[29,30] observed in preeclamptic patients also seems at odds with the observation of a lower heart rate in preeclamptic patients noted in our investigation[24] as well as that of Elvan-Taspinar et al.[25] Older literature,[31,32] in which pharmacologic autonomic blockade was used in preeclamptic patients, showed no effect on blood pressure, and thus is at odds with the aforementioned work of Schobel et al.[29] Recently, Greenwood et al,[30] by using the technique of microneurography, showed that in normal pregnancy sympathetic output was increased in women with normal pregnancy and even more so in a hypertensive pregnant group, while baroreceptor reflex sensitivity was impaired in both groups. It is possible that sympathetic activity in the peripheral nerves may not truly reflect that of centrally mediated sympathetic activity. Also, increased sympathetic activity may be a result rather than the inciting event in preeclampsia.

Alternatively, production or inhibition of circulating factors may be involved in these observations. A factor such as sFlt-1, in inhibiting vascular endothelial growth factor and placental growth factor, might trigger a cascade of events responsible for the cardiovascular changes in preeclampsia described in this review.[33] Hypoxia, nitric oxide, or a host of proinflammatory cytokines also might play a role in these changes.[34] A longitudinal study throughout pregnancy using our methodology as well as assessing circulating factors might help address the nature of the maladaption in cardiovascular response seen in preeclampsia. Additional factors influencing blood pressure control such as increased responsiveness to angiotensin II[28] or genetic factors[34] may be contributory.

Recently, an interesting report documented abnormal microvascular function in women 15 to 25 years after a pregnancy complicated by preeclampsia, comparing them with a cohort with normal pregnancies who did not display the dysfunction.[35] Whether the abnormality was endothelial in nature or dysfunction at the level of the vascular smooth muscle was not able to be determined.[35]

Interestingly, Spaanderman et al[36] studied normal and hypertensive women, both groups having had a history of preeclampsia, and normotensive controls who had had uncom-

plicated gestations, noting that in the nonpregnant state previously preeclamptic women had increased left ventricular work and lower plasma volume to lean body mass ratio but no differences in the levels of volume regulatory hormones (eg, renin, angiotensin II, atrial natriuretic peptide, or aldosterone). Spaanderman and colleagues[37] also noted that in those women becoming pregnant, that at 5 weeks gestation both controls and previously preeclamptic women, now normal or with chronic hypertension, had similarly decreased TVR, and at 7 weeks had no differences in carotid compliance or distensibility, but there was lower femoral arterial compliance and distensibility in those with previous preeclampsia. Although supporting our findings in normal pregnancy,[4] these results suggest that the normal adaptive mechanisms in pregnancy responsible for increased compliance are somehow impaired in those with a history of preeclampsia. It is tempting to speculate that the decreased global arterial compliance in preeclamptic gravidas[24] persists after pregnancy, possibly secondary to persistently altered responsiveness of the vascular smooth muscle tone or owing to irreversible changes in vascular wall remodeling. A longitudinal study design is required to answer this question.

Future Cardiovascular Implications for Preeclamtics

Several intriguing reports have suggested an increased risk for cardiovascular and thromboembolic events in women with a history of preeclampsia.[38,39] These studies are epidemiologic in nature, using population-based registries, and unable to distinguish whether these women had a predisposition to cardiovascular disease before gestation or whether preeclampsia incited cardiovascular damage that persisted and lead to these events. In one report a strong family history of aggregate cardiovascular risk increased the likelihood for developing preeclampsia 2- to 3-fold, supporting the idea that it is actually a predisposition to cardiovascular disease that leads to preeclampsia and subsequent heart disease.[40] Additional information regarding these hypotheses are needed.

Summary

A host of changes in the cardiovascular system are associated with the development of preeclampsia, which ultimately lead to the classic low cardiac output, high systemic vascular resistant state. The newer idea of a hyperdynamic, low-resistance disease state with its genesis early in pregnancy might support long-standing vascular damage that could persist into later life. Cardiac contractility is preserved in preeclampsia, but both steady and pulsatile arterial load are increased inappropriately (in other words, fails to decrease as would occur in normal pregnancy), involving both conduit and small vessels. Abnormal adaptive mechanisms may be secondary to changes in vascular tone or vascular wall elements, and may have future (ie, later in life) implications.

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