Gender Differences in Vascular Compliance in Young, Healthy Subjects Assessed by Pulse Contour Analysis

Nathaniel Winer, MD; James R. Sowers, MD; Michael A. Weber, MD

Objectives. Sex hormones exert important effects on the vasculature. Female sex hormones have been reported to enhance endothelial function, reduce oxidative stress, and protect against atherosclerosis. However, the effects of estrogen on vascular compliance have not been studied. Recently, noninvasive instrumentation that estimates vascular compliance by recording the radial artery pulse contour has been introduced. Reductions in the oscillatory or reflected component of the diastolic waveform have been observed in various clinical conditions, including hypertension, diabetes mellitus, and congestive heart failure, and may reflect endothelial dysfunction at the site of resistance vessels. In this study the authors examined gender-related vascular compliance in a cohort of young, healthy, predominantly nonsmoking, medication-free men and women to determine the influence of cardiovascular risk factors, including family and social history, serum lipids, plasma homocysteine, and insulin levels on vascular compliance.

Methods. The volunteers, consisting of 151 healthy men and women (mean age 24±4 years) completed a questionnaire detailing family and social history, medication use, and exercise habits. Large (C_1) and small (C_2) vessel compliance and various cardiovascular parameters were derived from arterial pulse wave contour analysis. Systolic, diastolic, and mean arterial blood pressure, pulse pressure, and pulse rate were determined simultaneously by oscillometry. Blood for fasting serum lipids, plasma homocysteine, and serum insulin were obtained in a subset of 135 subjects.

Results. The questionnaire revealed that 38% of parents had a history of hypertension, 31% had dyslipidemia, and 15% had coronary heart disease. C_2 was lower in subjects with parental dyslipidemia. Compared to men, women had lower C_2; lower systolic blood pressure, mean arterial pressure, and pulse pressure; higher serum high-density lipoprotein cholesterol; lower serum triglycerides; and lower plasma homocysteine, but similar serum insulin levels. C_1 correlated with height and pulse pressure, whereas C_2 was proportional to height and weight and inversely related to systemic vascular resistance. Multivariate regression analysis showed that stroke volume, total vascular impedance, cardiac output, female gender, and systemic vascular resistance independently predicted changes in C_2, but that height was not a significant factor.

Conclusions. Women have reduced C_2 despite lower systolic blood pressure and pulse pressure and more favorable lipid and homocysteine levels. C_2 is independent of height and is lower in subjects with parental dyslipidemia. These data indicate that female sex hormones have unexpected negative effects on small vessel compliance. They may help to explain why premenopausal women hospitalized for myocardial infarction have higher mortality rates than men of the same age. (J Clin Hypertens. 2001;3:145–152). ©2001 by Le Jacq Communications, Inc.

From the Department of Medicine, Division of Endocrinology, Diabetes, and Hypertension, SUNY Health Science Center at Brooklyn
Address for correspondence/reprint requests: Nathaniel Winer, MD, Professor of Medicine, Division of Endocrinology, Diabetes, and Hypertension, Box 1205, 450 Clarkson Avenue, Brooklyn, NY 11203
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It is now recognized that sex hormones play an important role in vasomotion and vascular remodeling. Estradiol, for example, has been shown to promote nitric oxide (NO)-mediated vasodilatation,

reduce vascular oxidative stress, and retard atherosclerosis.[1,2] However, discrepancies exist with regard to the general concept of vascular protection by estrogen. For example, estrogen treatment of male-to-female transsexuals decreases vascular compliance.[3] Moreover, in diabetics and women with pre-existing coronary artery disease (CAD), estrogen treatment fails to provide vascular protection and may increase vascular events.[4] Women are more likely to die following a myocardial infarction (MI) compared to men. One possible explanation for this phenomenon could relate to a higher prevalence of small vessel CAD in women.

Recently, a noninvasive instrument has been introduced that estimates vascular compliance by recording the radial artery pulse contour by tonometry.[5] The technique is based on a modified Windkessel model[6] that uses two compliance elements, C_1 and C_2, and inertance and resistance elements, analogous to an electrical circuit. With the use of a computer algorithm, the morphology of the arterial pulse contour can be separated into an exponential diastolic decay generated by the release of blood from the large arteries and a sinusoidal wave arising from peripheral wave reflections. The diastolic decay is a function of large artery compliance (C_1), while reflections or oscillations represent the compliance characteristics of the resistance vessels and branch points (C_2). A comparison of direct brachial artery cannulation with combined radial artery tonometry and oscillometric measurement of brachial artery blood pressure shows a close correlation of systolic, diastolic, and mean arterial blood pressure, and cardiac output with C_2 in subjects with well maintained cardiac output.[7]

Changes in both the function and structure of the arterial wall may occur before clinical signs and symptoms of atherosclerotic vascular disease become apparent.[8] Measurement of vascular elasticity has the potential to detect such changes early in the course of disease. Changes in the oscillatory or reflected component of the diastolic waveform have been observed with congestive heart failure (CHF),[9] postmenopausal estrogen replacement therapy,[10] hypertension,[11] aging,[12] cigarette smoking,[13] fish oil treatment,[14] and diabetes mellitus,[15] as well as in response to the administration of cardiovascular drugs.[16]

In this study, we examined vascular compliance in a cohort of young, healthy, predominantly nonsmoking, medication-free men and women in order to exclude potentially confounding risk factors. The purpose of the study was to determine the gender-related influence of cardiovascular risk factors, including family and social history, serum lipids, serum insulin, and plasma homocysteine on vascular compliance. We found a significant gender difference in vascular compliance and metabolic parameters in this young, healthy group.

METHODS

Subjects

One hundred fifty-one healthy volunteers were recruited after informed consent had been obtained. Subjects with a history of hypertension, hyperlipidemia, diabetes mellitus, or other cardiovascular disease were excluded, as well as those receiving medications (except for vitamins and oral contraceptives).

Design

Each participant completed a questionnaire detailing family and social history, medication use, and exercise habits. Large and small artery elasticity indices (C_1 and C_2) and estimates of systemic vascular resistance (SVR), total vascular impedance (TVI), stroke volume, cardiac ejection time, and cardiac output were derived from arterial pulse wave contour analysis recorded by tonometry over the right radial artery in the supine position. Systolic, diastolic, and mean arterial blood pressure, as well as pulse rate were determined simultaneously by oscillometry over the left brachial artery. Pulse pressure was calculated as the difference between systolic and diastolic blood pressure. Blood samples for fasting lipids, plasma homocysteine, and serum insulin were obtained in a subset of 135 subjects. Cardiovascular parameters were measured, with the HDI/Pulse Wave™ Research Cardiovascular Profile instrument, Model CR-2000 (Hypertension Diagnostics, Inc., Eagan, MN). Plasma total homocysteine levels were quantitated by high performance liquid chromatography with fluorescence detection.[17] Fasting lipid profiles were measured by standard clinical laboratory techniques. Plasma insulin was determined by radioimmunoassay (Coat-A-Count®, Diagnostic Products Corporation, Los Angeles, CA).

Statistical Analysis

Pairwise *t* tests and one-way analysis of variance determined correlations between categoric and continuous variables. Gender differences were evaluated by analysis of variance. Chi-square tests were used to determine whether there were gender differences in demographic parameters. Stepwise multiple linear regression models for C_1 and C_2 and cardiac and metabolic parameters were performed to determine independent predictors of change. JMP® statistical analysis software (Statistical Analysis Systems, Cary, NC) was used.

RESULTS

Demographic Characteristics

The study population consisted of 70 men and 81 women (Table I) with a mean age of 24±4 years (range 18–36 years), 72% of whom were white. Men were significantly heavier (178±33 lbs vs. 135±23 lbs; $p<0.001$) and taller (71±3 vs. 65±3 in; $p<0.001$) than women. In 57% of subjects both parents had cardiovascular disease, and 39% of subjects had parents with a history of hypertension; with nearly one in three had a parental history of dyslipidemia. Fewer than 10% had parents with a history of diabetes mellitus, stroke, or peripheral vascular disease. Over 80% exercised at least 30 minutes twice weekly, 8% smoked cigarettes, and >40% admitted occasional alcohol intake. More than 30% of subjects consumed vitamins regularly and almost 40% of women used oral contraceptives. In subjects with a parental history of dyslipidemia, mean small artery elasticity was 7.8±2.5 ml/mm Hg x 100 compared with 7±2.0 ml/mm Hg x 100 in those with no history of dyslipidemia ($p=0.029$) (Fig. 1). There was no significant difference in mean C_1 or C_2 between users and nonusers of oral contraceptives.

Metabolic Parameters

Women had higher serum high-density lipoprotein (HDL) cholesterol than men (59±13 vs. 49±13 mg/dL; $p<0.001$), lower serum triglycerides (87±40 vs. 106±61; $p<0.03$), and lower plasma homocysteine lev-

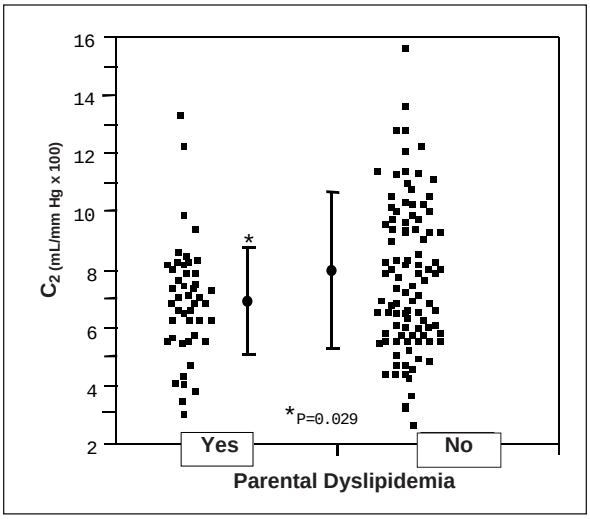

Figure 1. Small artery elasticity index and parental dyslipidemia.

TABLE I. DEMOGRAPHICS GROUPED BY GENDER

VARIABLES	TOTAL (N=151)	MEN (N=70)	WOMEN (N=81)
Race			
Black	9	2	7
White	109	53	56
Asian	31	13	18
Other	2	2	0
Age (yrs)	24±4	24±4	23±3
Weight (lbs)	155±35	178±33	135±23†
Height (in)	68±4	71±3	65±3†
PARENTAL HISTORY (N=149*)			
Hypertension	57 (38)	28 (40)	29 (39)
Dyslipidemia	46 (31)	17 (24)	29 (36)
CHD	22 (15)	16 (23)	6 (8)**
Diabetes	14 (9)	7 (10)	7 (9)
Stroke	7 (5)	1 (1)	6 (8)
PVD	3 (1)	2 (3)	1 (1)
SOCIAL AND MEDICATION HISTORY			
Smoking	11 (7)	7 (10)	4 (5)
Alcohol	63 (42)	33 (47)	30 (47)
Exercise	128 (85)	59 (84)	69 (85)
BCP	32 (21)	0 (0)	31 (38)
Vitamins	49 (32)	25 (36)	24 (30)

*Two subjects were adopted; **$p<0.01$; †$p<0.001$ percent shown in parentheses; CHD=coronary heart disease; PVD=peripheral vascular disease; BCP=oral contraceptives

els (5.3±1.4 vs. 7±1.9 pmol/L; $p<0.001$). Fasting serum insulin did not differ between genders (Table II).

Hemodynamic Variables

Mean systolic blood pressure, mean arterial pressure, and pulse pressure were significantly lower in women than in men ($p<0.01$ for each), but there was no gender difference in diastolic blood pressure or heart rate. Compared to their male counterparts, women showed significantly lower small artery elasticity ($p<0.001$) (Fig. 2) and higher SVR ($p=0.001$) (Table III). In contrast, large artery elasticity did not differ between the genders.

Correlations With C_1 and C_2

C_1 was directly proportional to height and pulse pressure ($r=0.32$; $p=0.001$ and $r=0.37$; $p<0.001$) and inversely proportional to TVI ($r=-0.79$; $p<0.001$), while C_2 correlated with both height and weight ($r=0.37$; $p<0.001$ for both) and was inversely related to SVR ($r=-0.43$; $p<0.001$). A parental history of dyslipidemia correlated weakly with small artery elasticity ($r=0.29$; $p<0.05$). There were no significant correlations between either C_1 or C_2 and lipid, homocysteine, or insulin levels (Fig. 3).

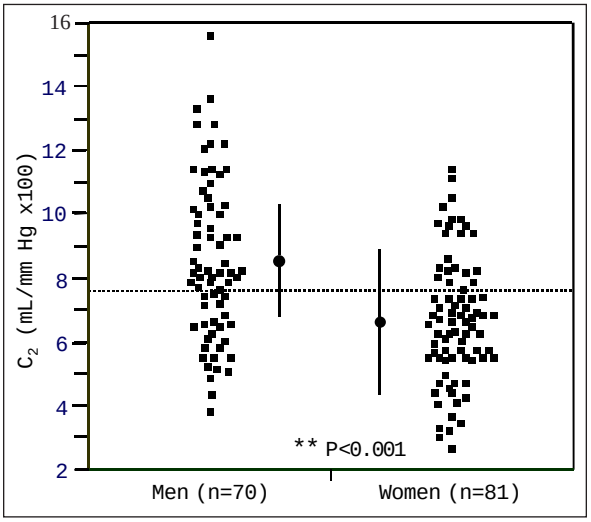

Figure 2. Small artery elasticity index in men and women.

Multivariate Analysis

To determine the independent predictors of the changes in large and small artery elasticity, a multivariate linear regression model was derived for large artery elasticity, entering gender, height, weight, SVR, TVI, cardiac output, stroke volume, and systolic, diastolic, and pulse pressure as variates. For small artery elasticity, a parental history of dyslipidemia, height, weight, heart rate, SVR, TVI, cardiac index, and stroke volume were used. Of the variables entered, TVI, cardiac output, and stroke volume independently influenced large artery elasticity, while SVR and pulse rate independently and negatively affected small artery elasticity; gender was of marginal significance (Table IV).

DISCUSSION

The present study shows that small artery elasticity is reduced and SVR is increased in young women, compared to age-matched, healthy men, despite women having lower systolic blood pressure and pulse pressure, higher serum HDL cholesterol and lower serum triglycerides, and reduced plasma homocysteine. In contrast, large vessel elasticity did not differ significantly between men and women.

The finding of reduced small artery elasticity in women seems counterintuitive, since premenopausal women are protected against the cardiovascular morbidity and mortality experienced by men of similar age; however, after menopause, women have a higher incidence of systolic hypertension,[18] a greater age-related increase in left ventricular hypertrophy,[19] and a higher incidence of CHF after MI, despite a smaller infarct size.[20] Even though women in the Studies Of Left Ventricular Dysfunction (SOLVD) had a lower incidence of ischemic heart

TABLE II. METABOLIC PARAMETERS GROUPED BY GENDER

Parameter	Total (N=142)	Men (N=66)	Women (N=76)
Cholesterol (mg/dL)	176±35	174±35	178±34
Triglycerides (mg/dL)	96±52	106±61	87±40*
HDL cholesterol (mg/dL)	54±14	49±13	9±13**
LDL cholesterol (mg/dL)	102±32	103±33	100±32
Homocysteine (µmol/L)	6.1±1.8	7.0±1.9	5.3±1.4**
Insulin (µIU/ml)	12.4±5.0	12.6±5.5	12.1±4.5*

*$p<0.03$; **$p<0.001$ women vs. men; LDL=low-density lipoprotein; HDL=high-density lipoprotein; IU=international unit

TABLE III. HEMODYNAMIC VARIABLES GROUPED BY GENDER

VARIABLE	TOTAL (N=151)	MEN (N=70)	WOMEN (N=81)
Systolic BP (mm Hg)	119±10	123±8	116±10**
Diastolic BP (mm Hg)	67±7	68±8	66±7
MAP (mm Hg)	84±8	86±8	83±8*
Pulse pressure (mm Hg)	52±8	55±8	51±7*
Heart rate (bpm)	68±11	68±11	69±10
C_1 (ml/mm Hg x 10)	15.7±5.2	16.6±5	15.1±5
C_2 (ml/mm Hg x 100)	7.6±2.4	8.6±2	6.8±2**
SVR (dynes/sec/cm^5)	1191±174	1125±132	1248±186**
TVI (dynes/sec/cm^5)	124±33	117±29	131±34*

*p<0.01; **p<0.001 (women vs. men); BP=blood pressure; MAP=mean arterial pressure; SVR=systemic vascular resistance; TVI=total vascular impedance

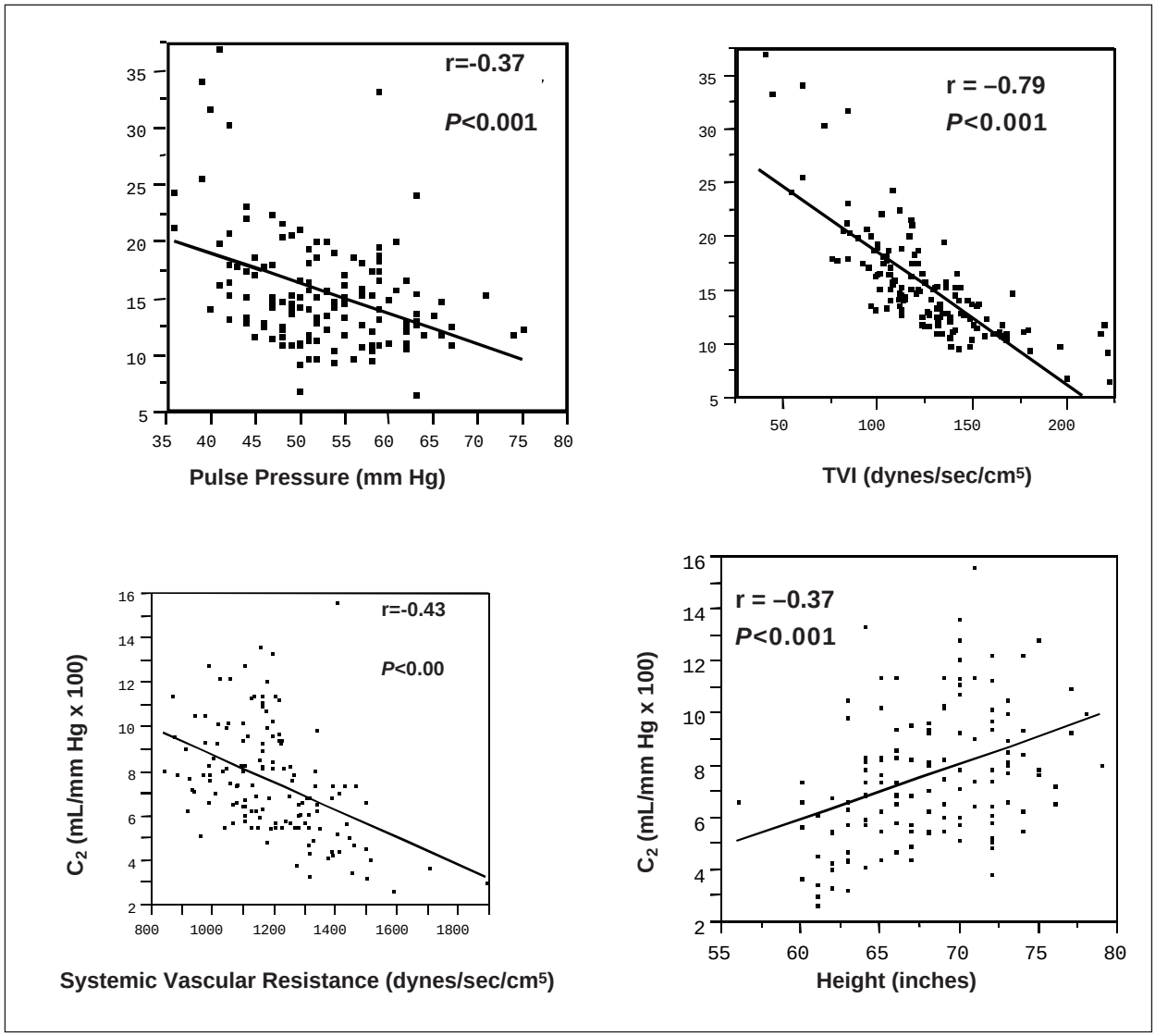

Figure 3. Relationships between large and small artery elasticity indices and other parameters. TVI=total vascular impedance

TABLE IV. STEPWISE MULTIVARIATE REGRESSION ANALYSIS WITH C_1 AND C_2 AS DEPENDENT VARIABLES

		Large Artery Elasticity (C_1)	
Variable	Regression Weight	*p*	r^2
TVI	-0.14	<0.0001	0.62
SVR	0.44	<0.0001	0.74
Cardiac index	-7.17	<0.0001	0.80
Heart rate	0.11	0.008	0.81
Homocysteine	-0.27	0.013	0.82
		Small Artery Elasticity (C_2)	
Variable	Regression Weight	*p*	r^2
Stroke volume	0.09	<0.0001	0.3
TVI	-0.02	<0.0001	0.39
Cardiac output	-1.51	<0.005	0.42
Gender	-0.61	<0.0002	0.47
SVR	0.0	<0.003	0.50

The following parameters were entered into the model for C_1: cholesterol; triglycerides; high-density lipoprotein cholesterol; homocysteine; insulin; height; weight; systolic, diastolic, mean arterial, and pulse pressure; heart rate; systemic vascular resistance (SVR); total vascular impedance (TVI); cardiac output; cardiac index; ejection time; stroke volume; and stroke volume index. In addition to these parameters, parental dyslipidemia and gender were included in the model for C_2.

disease than men, their mortality and hospital admission rates were greater than those for men.[21] The notion that higher HDL cholesterol and lower serum triglyceride levels afford cardiovascular protection for premenopausal women compared to men of similar age may not be universally true. A recent study of a database of >384,000 patients from the National Registry of Myocardial Infarction[22] indicates that during hospitalization for MI, women <50 years of age had double the mortality rate as men of the same age; moreover, the younger they were the greater the risk of death. Differences in medical history, severity of infarction, and early management accounted for only about one third of the difference in risk.

The pathophysiology of coronary heart disease (CHD) in premenopausal or middle-aged women may differ from that of older women and men because plaque erosion, rather than plaque rupture, is more common in premenopausal women who die suddenly,[23] and coronary artery narrowing is less in younger women who have a MI, die suddenly of cardiac causes, or survive a cardiac arrest.[24] Young women are more likely to have transmural MI with normal findings on coronary angiography[25] and may have associated vasospastic syndromes, such as migraine and Raynaud's phenomenon.[26] Syndrome X, diagnosed in patients who have exertional angina, a positive response to exercise testing, and angiographically normal coronary arteries is also found predominantly in postmenopausal women.[25]

A recent study of patients presenting with acute coronary syndromes[27] indicated more pre-existing conditions and greater severity of clinical abnormalities in young women compared to young men, including a higher Killip class, a higher pulse rate, and a lower systolic blood pressure, differences not found between older women and older men. Yet fewer young women presented with ST segment elevations, despite having similar infarct locations, creatine phospokinase levels, and ejection fractions. Women had higher rates of complications during hospitalization, including hypotension, heart failure, shock, and bleeding. Women were more likely to have unstable angina than acute MI, and of those that had MI, fewer women than men presented with ST segment elevation. Women with MI and ST segment elevation did worse than men with similar findings. Women undergoing coronary angiography were less likely to have clinically significant coronary disease. The findings in these two studies suggest that women are protected from the development of atherosclerotic disease or that its progression is delayed or modified. The increased prevalence of unstable angina without occlusive coronary disease among women suggests that abnormal vasomotor tone, minimally atherosclerotic epicardial arteries, or a hypercoagulable state may trigger a MI in younger women. Healthy, young adults (mean age, 25 years) with a family history of coronary disease, but without other cardiovascular risk factors, have impaired endothelium-dependent

vasodilatation.[28] It is possible that endothelial dysfunction may play a role and manifest early in life. The reduction in C_2 may reflect endothelial dysfunction at the smaller resistance vessels, since intravenous infusion of the NO synthase analogue NG-nitro-1-arginine methyl ester (L-NAME) into healthy subjects reduces C_2 and increases blood pressure without affecting C_1.[29] Women who have a MI and greater morbidity and mortality than men of the same age may lack a protective factor, such as estrogen normally present in women, especially since the gender difference in coronary outcome diminishes with age. One of the mechanisms by which estrogen reduces vasoconstriction is by stimulating the release of NO and prostacyclin.[30]

Data on gender differences in vascular compliance are contradictory. Several studies indicate that men have reduced compliance compared to premenopausal women.[31–33] In contrast, ultrasound measurement of carotid artery compliance and estimation of systemic arterial compliance by pulse pressure waveform analysis suggest arterial stiffness is greater in women than in men.[34] Short-term administration of ethinyl estradiol combined with an antiestrogen to young male-to-female transsexuals increased compliance and distensibility of the femoral and brachial arteries, whereas treatment of female-to-male transsexuals with testosterone had no effect on these parameters.[3] Many of the physiologic differences between men and women, including vascular function, lipid profiles, coagulation, and fibrinolytic systems, are attributable to estrogen.[35] The absence of a difference in C_1 between users and nonusers of oral contraceptives in the present study does not exclude an estrogen effect, since women in this age group would be expected to have abundant estrogen stores. Moreover, vascular compliance is unchanged during various phases of the menstrual cycle,[36] but is greater in postmenopausal women receiving estrogen replacement therapy than those who remain estrogen-deficient.[37] Understanding gender differences is important and should not only improve treatment for women, but also permit application of appropriate therapeutic measures to the entire population.

Since both body weight and height were significantly lower in women, part of the observed gender difference in small vessel compliance could be due to the smaller body size of the female group. An analysis of the carotid pulse wave contour[34] found that the late systolic peak or "augmentation index," which is thought to represent reflected waves, is higher in women, increases with aging, and is inversely proportional to body height. Reflected waves are more prominent in women because of shorter distance to reflecting sites and increased aortic tapering. A multiple linear regression model showed that of the independent predictors of change in augmentation index, gender was the strongest determinant, but age, heart rate, mean arterial pressure, carotid maximal rate of pressure rise (dP/dtmax), and height also exerted an influence.[34] Although height was inversely correlated with the augmentation index in both men and women, the fact that the increase in the augmentation index occurred from the first decade decreases the likelihood that vascular stiffness plays a role in systolic augmentation. Gatzka et al.[38] found that among 101 pairs of elderly hypertensive women and men who were matched for height, gender differences in wave reflection were independent of body height. Stepwise multivariate analysis in the present study failed to show body height as an independent influence on small vessel compliance. Although there are no published studies addressing the relationship between small vessel compliance as estimated by arterial pulse contour analysis and reflected waves as measured by the augmentation index. Resnick et al.[39] reported a close correlation of both C_1 and C_2 with the stroke volume/pulse pressure ratio, based on pulse contour analysis data, and of C_1 with magnetic resonance imaging-determined aortic distensibility.

Hyperhomocysteinemia has been established as a significant cardiovascular risk factor even at plasma levels within the upper quintile of the normal range.[40] Plasma total homocysteine levels were slightly but significantly lower in women compared to men, consistent with previous reports.[41] Plasma homocysteine also increases with age and may be lowered by vitamins containing folic acid. About one in three of our subjects was taking a vitamin supplement, which may have lowered mean homocysteine levels.

The current study demonstrates a correlation between a parental history of dyslipidemia and small artery compliance. Weber et al.[42] reported that normotensive relatives of individuals with hypertension have reduced small vessel compliance. Similarly, healthy, young adults with a family history of premature coronary disease and no other cardiovascular risk factors may have impaired endothelium-dependent vasodilatation.[28] Longitudinal studies will be required to determine the potential of arterial pulse contour measurements to predict future cardiovascular risk in both men and women.

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